

European AIDS Conference Sheds Illusions about HIV Therapy

by Kristen Kresge

By location alone, the 9th European AIDS Conference (EACS) in Warsaw, Poland instantly set itself apart from other HIV/AIDS conferences this year. Dr. Andrzej Horban — co-chair of the conference and director of the Hospital of Infectious Diseases in Warsaw — delivered the opening comments and welcomed delegates from around the world to the first AIDS conference ever to be held in Eastern Europe.

Eastern Europe has experienced a burgeoning HIV/AIDS epidemic in recent years. In countries like Russia and the Ukraine, HIV has quickly exploded among young intravenous drug users. The Ukraine, Poland's neighbor to the east, has the highest prevalence of HIV among adults in all of Europe — a staggering 1% when compared with large countries like France, which have a prevalence of only 0.4%. The countries of Eastern Europe, along with central Asia, are experiencing the fastest growing epidemic in the world, making Warsaw an appropriate location for researchers to gather and discuss the latest research on HIV.

Even more significantly, Poland was hosting the meeting on the eve of its entrance into the European Union. Far in advance of the International AIDS

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New drugs were not the main attraction at last October's EACS. Read about how this conference illuminated novel ways to treat HIV with already approved drugs.

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New data from the EuroSIDA cohort reveal that hepatitis B and C are both affecting HIV-positive people at alarming rates. Get the details about the research presented at EACS.

Conference in Thailand, EACS was east meets west on European ground. Ideas and trends in treating and managing HIV infection became the focus. The conference at times succeeded in challenging some of the basic dogmas of therapy and brought some fringe ideas to the forefront of debate.

More Isn't Always Better

You might say that it has been a tough year for Trizivir. The one tablet combination of three nucleoside analogs (zidovudine [AZT], lamivudine [3TC], and abacavir) is a simple and attractive option for doctors seeking to avoid the side effects involved in combining drugs from different classes, and it is the only way that some patients will agree to take any medication. But Trizivir's role as a sole treatment for HIV has been seriously questioned. Earlier this year the ACTG 5095 study,

comparing Trizivir alone with the combination of Trizivir and the potent non-nucleoside efavirenz (Sustiva), found that adding efavirenz was much more effective than Trizivir alone. Fewer people taking Trizivir by itself were able to suppress the virus, and this group failed therapy earlier than the participants who were also taking efavirenz. Twice as many people taking Trizivir alone had detectable viral loads within eight months of starting therapy.

These results led the National Institutes of Health, the sponsors of the study, to discontinue the Trizivir-only arm. Soon after the initial reports of this trial garnered attention, another study involving a triple nucleoside regimen met a similar demise. In October, Gilead Sciences (tenofovir's manufacturer) announced high failure rates in people receiving the triple NRTI regimen of didanosine (ddI), 3TC, and tenofovir. In a 24-week, Gilead-sponsored trial, 24 people naive to HIV therapy were given this drug combination and 91% of them were classified as failures because they did not have substantial reductions in viral load by the twelfth week. Gilead issued a letter to physicians recommending that tenofovir, in combination with ddI and 3TC alone, not be used in patients with HIV.

An additional report at EACS only added to questions about the role of Trizivir in HIV treatment. Dr. Schlomo Staszewski of Goethe University in Frankfurt presented the interim results from the QUAD study (abstract F1/1), which compared Trizivir with Combivir when either was taken with a ritonavir-boosted protease inhibitor. The goal of this study was to match a three-drug regimen of Combivir (AZT and 3TC) and boosted saquinavir against a four-drug regimen of Trizivir and boosted saquinavir. By boosting saquinavir with small amounts of ritonavir, the level of saquinavir in the body increases and the drug becomes more potent.

The QUAD study included 59 people who had no prior exposure to HIV drugs but had high viral loads (an average 300,000 copies/mL) and low CD4 counts (between 22 and 31 cells/mm³) at the start of the study. After 24 weeks both groups had made similar progress, experiencing declines in viral load and higher CD4 cell counts. In each group 60% of volunteers had undetectable viral loads. No significant differences of any kind occurred between Trizivir and Combivir. Staszewski concluded that there was no benefit to having four drugs instead of three. This led him to ask what Trizivir is worth — since it cannot be used alone and is not any better than Combivir when the latter is used in combination with another drug.


Dr. Myrto Astriti of Hôpital Pitié-Salpêtrière in Paris, whose oral abstract followed Staszewski's, attempted to answer this question. Speaking in Trizivir's defense, Astriti presented a retrospective study of 120 patients who received Trizivir as their initial HIV therapy (abstract F1/2). At the start of treatment, volunteers had an average viral load of approximately 83,000 copies/mL. After two years on Trizivir alone, 58% of participants had viral loads below 200 copies/mL. Only 15% of the people evaluated were considered Trizivir failures, and most of these people reportedly did not take their prescribed medicine. Astriti's data argued against rushing to judgment on Trizivir.

"Fifty percent of patients over two years of treatment still doing well," said Astriti. "This is something we shouldn't forget."

But Is Only One Enough?

While doubts about Trizivir persisted, research continued to support the value of Kaletra, a protease inhibitor that boosts the drug lopinavir with ritonavir. In a study comparing once-daily Kaletra with twice-daily Kaletra, in combination with tenofovir and emtricitabine (FTC), Dr. D. Podzamczar of Hospital Bellvitge in Barcelona reported that there was no difference between doses at 24 weeks (abstract F1/3). Of 190 volunteers, 115 received 800 mg of lopinavir with 200 mg of ritonavir, or eight pills, once daily. The remainder received 400 mg and 100 mg respectively, or four pills, taken twice daily. After six months, 57% had undetectable viral loads in both groups. The rate of adverse events was higher in the once-a-day group, perhaps due to the high peak concentration of drug in the blood. But the level of adherence was lower in the twice-a-day group.

The significance of this study extended beyond Kaletra. These were the first clinical results for Gilead's fixed-dose combination of tenofovir and



"The best therapy is less or no therapy"

FTC. In addition to Kaletra, volunteers in this study received the double NRTI combination, which Gilead is currently developing as a single pill. This combination is expected to provide stiff competition for Combivir and another much anticipated combination containing abacavir and 3TC. Though the tenofovir/FTC duo will be the last to hit the market, it will be the only one available as one pill, once a day.

Researchers continue to focus on simpler drug regimens like fixed-dose combinations. Interest is growing in Kaletra as a potential single therapy for people reluctant to take on complex regimens, but willing to accept one medication. Dr. Joe Gathe presented a poster at the Interscience Conference on Antimicrobial Agents and Chemotherapy earlier this fall that reported results from a small group of patients at his private clinic who were taking only Kaletra and doing well (see the December 2003 *Treatment Insider*, “A Mishmash of Data at ICAAC”). EACS offered more new data on Kaletra monotherapy, in the form of an oral presentation entitled “Lopinavir/r as Sole Therapy for HIV Infection.”

The presentation by Dr. Gerald Pierone, of the AIDS Research and Treatment Center of the Treasure Coast in Florida, focused on a retrospective analysis of 15 people who had received Kaletra monotherapy for at least eight weeks at his clinic (abstract F1/5). In this small cohort, 13 people continued to receive Kaletra as their only therapy for an average of 68 weeks (the range was 39 to 104 weeks). In fact, 12 of the 15 people, or 80%, had viral loads below 400 copies/mL. The majority of this group (10 of 12) was below 75 copies/mL.

For the three patients whose viral loads did not decline to at least 400 copies/mL, resistance data are available. One person had the L63C mutation, while the other two had the L63A and V77I mutations. One person with double mutations was known to be non-adherent to the medication. There is still no evidence of resistance in the group that has successfully stayed on only Kaletra for as long as two years.

Although Dr. Pierone is enthusiastic about these data, he warns against making any presumptions about Kaletra's use as a monotherapy. “We have to be careful when drawing conclusions from small, retrospective studies with fifteen people. We need large, prospective studies with 100 or 200 people,” said Pierone.

And Pierone will get his wish. Abbott, the company that manufactures the drug, is initiating a large study of Kaletra monotherapy. This trial will explore what is called an induction/maintenance approach to Kaletra use. Volunteers will begin by taking Combivir

and Kaletra. Once they have sufficiently suppressed their viral loads (to less than 50 copies/mL for three consecutive months), they will be taken off of Combivir and remain on only Kaletra. If at any time they are failing Kaletra monotherapy, another drug will be added to maintain a suppressed viral load.

The study is designed to follow volunteers for up to 96 weeks and will include 150 people from sites around the world. The Kaletra monotherapy group will be compared with a separate reference group who will receive Combivir and efavirenz, a combination therapy that excludes protease inhibitors, for the duration of the study. Abbott is excited about the recent results and is hoping that this larger trial will reach the same conclusions, but they are careful with their recommendations.

“The monotherapy results from Gathe and Pierone are very promising. We now have a protocol and we're looking to initiate sites globally. We're encouraged that there's a good chance for success, but by no means would I endorse this as a wholesale clinical method,” said Scott Brun, global project head of antiviral development at Abbott Laboratories.

The risk with using only Kaletra is the potential for developing resistance. According to Mike Youle, a physician at the Royal Free Hospital in London, it would be “very unwise” to consider this strategy with the limited data that are currently available. He warns that HIV may become resistant to Kaletra more slowly than other drugs, but that resistance is still possible. Volunteers taking Kaletra as monotherapy therefore need to be monitored very closely for signs of virologic failure, so that they do not develop resistance to the entire class of protease inhibitors.

But if there ever were a drug that could be used as monotherapy, it would be Kaletra, according to Youle. HIV must undergo several mutations before developing resistance to Kaletra, posing a high barrier for the virus to surmount. This is not true for all antiretrovirals. A single mutation can confer resistance to efavirenz, resulting in virus resistant to the entire non-nucleoside class.

“In our clinical trials we haven't seen resistance [to Kaletra] develop. That's not to say that it never will,” said Brun of Abbott. “It's not something you want to go out and do unless you have a really good understanding of the drug,” he added, referring to the monotherapy trial.

Abbott feels confident in its understanding of Kaletra after presenting long-term results of the drug in 100 treatment-naive volunteers. In a poster at EACS (abstract 7.3/16), Abbott reported that after five years,

64% of people taking Kaletra along with stavudine (d4T) and 3TC had undetectable viral loads. Through 252 weeks of follow-up in people whose viral loads rebounded on Kaletra, no protease inhibitor resistance was seen.

Continuing on the road to simplifying the treatment of HIV infection, the 9th EACS highlighted not

only new combinations of drugs, but also the reversal of an ideology that has existed since the introduction of HAART. Doctors are now looking at using fewer drugs, instead of adding more drugs on to existing regimens. “The best therapy is less or no therapy,” said Dr. Jose Gatell from the Hospital Clinic in Barcelona.

Dim Outlook for Hepatitis C Treatment

by Daniel Raymond

The field of hepatitis C therapy received a welcome boost with the arrival of two new forms of the drug interferon alfa — Schering-Plough’s Peg-Intron and Roche’s Pegasys. A process called pegylation allowed the injectable drugs to be used once a week, instead of the thrice-weekly injections required by standard interferon. Moreover, when combined with ribavirin, the makers of pegylated interferons boasted success rates of over 50% in sustaining undetectable HCV viral load levels, equating to a probable cure. Marketing materials touted “the power of pegylation.”

But cumulative clinical experience and recent reports from the annual meeting of the American Association for the Study of Liver Diseases (AASLD) have shifted from optimism to a more sober recognition of the therapy’s limits and realities. Particularly vexing are questions about the treatment’s effectiveness in people with HIV and in African-Americans; accompanying side effects such as anemia and depression; and the management of people with histories of substance abuse.

HCV coinfection has become an increasing concern for people with HIV. David Nunes of Boston University reported results from an ongoing study on the impact of HIV coinfection on HCV disease (abstract 602). The data revealed more advanced liver disease and liver disease-related deaths in people with HIV compared with those infected with HCV alone. Among 167 coinfecting individuals followed for at least one year, eight of fourteen deaths were from liver disease. Only one death was from liver disease among the 111 people infected only with HCV.

These findings parallel those reported in other studies in recent years, which document accelerated liver disease in coinfecting people. Since more people are dying of liver disease in the era of antiretroviral therapy, finding effective treatment for coinfecting

people has become urgent. But preliminary analyses from three large studies of pegylated interferon/ribavirin treatment in people with HIV have not been encouraging. The key measure of treatment success is a sustained virologic response, defined as an undetectable HCV viral load six months after ending therapy. Since many patients who initially respond to treatment later experience viral rebound, sustained virologic response rates are invariably lower than response rates reported in the middle and at the end of therapy. The 24-week results from Adult AIDS Clinical Trial Group’s 5071 study, reported in 2002, showed that 66 participants treated with Peg-Intron/ribavirin had a response rate of 44% halfway through the course of treatment. But experts predict this will translate into a sustained response of around 30%. Even without final results, it is becoming increasingly clear that fewer coinfecting people will have sustained responses than persons with HCV alone.

The 48-week data from the French RIBAVIC trial revealed an end-of-treatment response rate of only 37% in volunteers treated with Peg-Intron and ribavirin. RIBAVIC had a high dropout rate, with only 89 of the original 206 participants completing the full course of this treatment, and 23% experiencing significant adverse events. As with A5071, an even lower proportion of the coinfecting patients in RIBAVIC will likely have sustained responses, due in part to higher dropout rates and more difficulty tolerating therapy.

The final analyses of these studies will report on data from individuals followed for an additional 24 weeks after they complete 48 weeks of treatment. The results from these studies and from APRICOT — a multicenter trial evaluating Pegasys and ribavirin in coinfecting participants — are expected in the spring of 2004. “The 11th Conference on Retroviruses and Opportunistic Infections will be the

hot ticket,” predicts Mark Sulkowski of the Johns Hopkins Viral Hepatitis Center.

Treatment by the Numbers

In the meantime, October’s AASLD meeting offered a wealth of research on HCV mono-infection that tempered previous optimism about treatment. A large multicenter study conducted by the Veterans Administration (VA) illustrates some of the current dilemmas for people chronically infected with HCV. Edmund Bini of the VA Medical Center in New York evaluated 4,364 veterans with HCV, 7% of whom were coinfecting with HIV (abstract 603). Using the VA’s HCV Treatment Guidelines, only 25% were eligible for treatment, based on clinical criteria and exclusions for substance abuse, psychiatric illness, and other medical conditions. Nearly half of those offered treatment declined, citing side effects and the desire to wait for more effective treatment options.

Norbert Bräu of the Bronx VA Medical Center presented results from another VA study, in which 813 veterans had worse responses to standard interferon and ribavirin than people in previous phase III trials (abstract 1009). Over half of patients stopped treatment early, and the sustained virologic response rate was only 17%. African-Americans had the lowest response rate, a dismal 7%.

African-Americans generally have poorer responses to HCV treatment. Lennox Jeffers of the Miami VA Medical Center presented data on 78 African-Americans and 26 Caucasians who took Pegasys and ribavirin for 48 weeks (abstract 71). All had genotype 1, the strain of HCV considered hardest to treat (people with HCV genotype 2 or 3 only require 24 weeks of treatment). Only 26% of African-Americans had sustained responses, compared with 39% of Caucasians.

The African-American participants were more likely to have higher pretreatment HCV viral loads — associated with a poorer response to therapy. Of participants with high baseline HCV viral loads, only 20% of African-Americans and 25% of Caucasians had sustained responses to treatment. However, William Cassidy from Louisiana State University reported that a greater proportion of African-Americans in the Jeffers study experienced improvement in liver fibrosis after therapy — 25% versus 6% of Caucasians — in an analysis of 69 people who underwent biopsies before and 24 weeks after treatment (abstract 307).

Other analyses of this same study attempted to tease out the source of the differences. Charles Howell from the University of Maryland looked at differences in response by measuring changes in levels of interferon-stimulated genes in African-Americans. He found no overall correlation between gene expression levels and response to treatment (abstract 190). The NIH is conducting a 400-person trial, dubbed VIRAHEP-C, to examine why African-Americans respond differently to treatment than Caucasians, but final results will not be available until 2006. In the meantime, Jeffers recommends studying the effects of treating African-Americans with a higher dose of interferon.

Howell also found no significant differences in adherence to regimens between the groups, defined as taking at least 80% of the original prescribed dose over the duration of treatment (abstract 332). Eighty-six percent of African-Americans and 89% of Caucasians were adherent, with about 80% of each group completing the full course of therapy. However, more African-Americans lowered their Pegasys doses (46% vs 29% in Caucasians), mainly due to neutropenia. This may reflect the lower average neutrophil counts of African-Americans; in this study, African-Americans had lower baseline neutrophil levels, and their levels dropped faster during treatment than did those of Caucasians. Similar proportions in both groups (40%–46%) had to adjust the ribavirin dose, mainly due to anemia.

Managing anemia also poses significant challenges for treating HCV. Ribavirin-induced anemia, diagnosed by a drop in hemoglobin levels, is commonly treated by lowering the dose, which potentially weakens the therapy’s effectiveness. Some clinicians use erythropoietin to treat anemia during ribavirin therapy and allow full ribavirin dosing, but this drug’s impact on treatment outcome is unclear. Lauren Senkbeil from New York-Presbyterian Medical Center studied 50 people treated with Peg-Intron and ribavirin; 16 needed to lower the ribavirin dose for an average of 10 weeks (abstract 1213). Fourteen of these participants were given erythropoietin, all but one of whom resumed taking the original ribavirin dose. Sustained response rates were similar to those who maintained full-dose ribavirin throughout the course of therapy, suggesting a benefit to erythropoietin in managing anemia. But fewer people requiring a reduced Peg-Intron dose had sustained responses, even when prescribed granulocyte colony-stimulating factor in order to resume the original Peg-Intron dose.

Spotlight on Hepatitis in Warsaw

by Kristen Kresge

Concern over the increasing prevalence of HIV and hepatitis coinfection was evident at the 9th European AIDS Conference in Warsaw, Poland. Researchers reported a high rate of hepatitis C virus (HCV) coinfection in an analysis of the EuroSIDA cohort, a large group of HIV-positive Europeans. The EuroSIDA cohort follows up to 10,000 volunteers in 26 European countries and Argentina. Data from this group were presented during several plenary sessions at the meeting.

Dr. Jürgen Rockstroh from the University of Bonn in Germany spoke about the escalating rates of HCV coinfection (abstract F12/4). In a subset of the EuroSIDA cohort consisting of approximately 2,500 people with HCV serology data available, the overall rate of HCV was 34%. This figure is particularly alarming since HCV infection is still on the rise. The numbers were even higher in certain geographical subsets of the EuroSIDA group, which is divided into central, east, north, and south Europe. HCV coinfection was most widespread in the Eastern European coun-

tries, where the rate extended to 48%, most likely due to the high number of intravenous (IV) drug users in this region. HCV is most commonly spread through blood products and is transmitted readily by shared syringes. Overall in this cohort, 76% of participants who tested positive for HCV used IV drugs.

Although coinfecting people are more likely to progress to AIDS, or even die, coinfection did not seem to impact the volunteers' response to HIV treatment with highly active antiretroviral drugs. EuroSIDA data indicated that people with HIV/HCV were just as likely to have undetectable viral levels as persons with only HIV. Similarly, coinfection with HCV did not impact the gains in CD4 cells. This point adds further clarity to the controversy over the impact of HCV on HIV therapy, as several previous studies have found contradictory results. The authors of a study published on HCV within the Swiss HIV Cohort reported that coinfection was associated with smaller gains in CD4 counts after starting antiretroviral therapy. But the

Depressing News

Along with anemia, depression is a common side effect of HCV therapy, and can manifest as a symptom of chronic HCV infection itself. Depression is typically ascribed to interferon treatment, although some evidence suggests that ribavirin may also play a role. Several reports documented high rates of depression before and during HCV treatment. A study of 1,500 California Medicaid patients by Jeffrey Markowitz and Elane Gutterman from Health Data Analytics found that about half of patients with diagnosed HCV had been prescribed antidepressants (abstract 981). Importantly, about 85% of these patients were treated for depression *before* receiving an HCV diagnosis. This group was also more likely to receive interferon treatment following diagnosis. The authors pose two possible scenarios: people prone to depression may also be prone to HCV infection, or HCV itself contributes to depression.

Although not a component of the California Medicaid study, others have looked at the likelihood of treating depression in people with HCV. Paul Kwo of the Indiana University School of Medicine examined potential differences or biases in the prescribing practices of individual doctors, and has

linked antidepressant use and clinical experience with HCV treatment (abstract 1225). He analyzed data from 792 people who took standard interferon and ribavirin. Before starting treatment, 24% of patients were already taking antidepressants, and a significant portion of the remainder received antidepressants throughout the course of therapy. Of the 84 investigators involved in the study, those who had previously treated 100 or more patients for HCV were more likely to prescribe antidepressants during therapy.

Depression can be debilitating and even life threatening; a fairly small but disturbing number of suicides have been reported in HCV treatment studies. Depression may also affect adherence, but its impact on treatment efficacy is unknown. Charles Raison from Emory University in Atlanta followed 102 people undergoing HCV treatment and observed that patients who experience more symptoms of depression during therapy were less likely to have a sustained response to treatment (abstract 344). In contrast, another study by Jennifer Moss at New York-Presbyterian of 55 volunteers receiving Peg-Intron/ribavirin therapy uncovered a link between response to treatment and increased depression (abstract 1206). The authors speculate that both

analysis from the EuroSIDA cohort, which includes a larger number of volunteers and the longest period of follow-up, found no effect of HCV on CD4 count and may end the debate.

Outside of the EuroSIDA cohort, there were also several reports at EACS of a recent increase in sexual transmission of HCV throughout Europe. The traditional school of thought is that the virus is more likely transmitted through blood than semen or vaginal fluids, but according to an oral abstract from the Chelsea and Westminster Hospital in London, sexual transmission is on the rise.

Dr. Brian Gazzard presented results from a study involving a group of HIV-positive men at this London clinic, and concluded that in recent months an outbreak of HCV has occurred after reports of unprotected anal sex (abstract F12/3). Of 38 men in the last 18 months that had acute HCV, 15 were also diagnosed with syphilis within the previous year. Many of these volunteers experienced spontaneous regression of HCV and did not require antiviral drugs to clear the virus. Since transmission of HCV among men having sex with men increased dramatically in 2002 and 2003

across all of Europe, researchers have become concerned that HIV-infected males are engaging in more high-risk behavior.

Turning attention to the hepatitis B virus (HBV), Dr. Stephane De Wit of the Saint-Pierre University Hospital in Brussels presented data on the prevalence of HBV among HIV-infected individuals in the EuroSIDA cohort (abstract F9/3). A much smaller epidemic of HIV/HBV coinfection exists in Europe — only 9% of the nearly 6,000 patients in this subset are coinfecting. Still, coinfection with HBV was found to cause a higher rate of liver-related mortality in people with HIV. As with HCV, however, this analysis showed that HBV did not impact a person's response to HAART; volunteers with HBV had the same drops in viral load and gains in CD4 cells as those with only HIV.

Both HBV and HCV coinfecting members of the EuroSIDA cohort will continue to be followed to evaluate the impact of viral hepatitis on HIV. Since the inclusion of Eastern European countries into the EuroSIDA cohort, this research has become extremely important in the effort to monitor the quickly growing epidemic in this region of the world.

treatment-related depression and virologic response may be biologically interconnected.

Depression may be a particular problem for people coinfecting with HIV, suggests Kenneth Sherman of the University of Cincinnati. "We have a study funded by the NIH that examines this issue. My sense is that depression is more common with coinfection, but the data have not yet been fully analyzed," says Sherman.

Managing depression is also a significant issue for HCV treatment in people with histories of injection drug use, most of whom are infected with HCV. Rates of depression and other kinds of mental illness in this group can run as high as 50%. Marcus Schaefer at Berlin's Humboldt University treated 11 controls with no history of psychiatric illness and 25 methadone patients with interferon and ribavirin (abstract 333). Fourteen participants on methadone began taking the antidepressant citalopram (Celexa) two weeks before beginning treatment. While the incidence of major depression episodes was relatively high, and similar between the control group and the methadone patients who did not receive citalopram (55% and 64%, respectively), only 14% of methadone patients taking citalopram experienced a major depressive episode.

Another methadone study reported by Stefan Mauss of the Center for HIV and Hepatogastroenterology in Düsseldorf compared HCV treatment outcomes in 50 people on methadone maintenance and a control group of 50 persons with no history of injection drug use or methadone within the last five years or more (abstract 1218). Sustained response rates did not differ significantly between the two groups (39% methadone vs 54% control). A greater number of methadone patients dropped out within the first two months of treatment (11 vs 2 controls), but 50% of those who continued therapy beyond that time had sustained responses, compared with 56% of controls.

Despite favorable response rates and tolerability in pilot studies of HCV therapy for methadone patients, many people with substance abuse histories — particularly current drug users — do not receive treatment for HCV. This issue formed the focus of a November meeting sponsored by the National Institute on Drug Abuse and other federal agencies. Researchers and clinicians presented data and strategies on managing HCV in current and former drug users, emphasizing the low incidence of reinfection with HCV following successful treatment, the relatively good adherence to treatment, and the use of antidepressants to manage psychiatric side effects.

The meeting was partially a response to the history of excluding substance users from HCV treatment. A 1997 NIH-sponsored consensus statement recommended that treatment be withheld until people are abstinent from drugs and alcohol for at least one year, primarily due to concerns about adherence and reinfection from continued injection drug use. In 2002 this recommendation was reversed in a new consensus statement, which recommended that substance users be evaluated on a case-by-case basis, but the meeting's participants emphasized that clinical practice has not caught up with this change. "In what other disease is the group most likely to be infected the least likely to be treated?" asked Sharon Stancliff of the New York State Department of Health's AIDS Institute.

In the meantime, the numbers of people undergoing HCV treatment remain relatively flat, at 100,000 per year according to drug company data. Schering-Plough, the manufacturer of Peg-Intron, has seen its market share eroded by competition from Roche's Pegasys, and will probably see even less profits after the launch of generic ribavirin in the coming months. In response, Schering announced plans for a 2,880-person clinical trial, the IDEAL study, comparing Peg-Intron with Pegasys when each is combined with ribavirin in people with HCV genotype 1. The study will also compare high- and low-dose Peg-Intron, fulfilling a post-marketing commitment made after the FDA approved the drug.

Paging Protease Inhibitors

Regardless of IDEAL's outcome, many people with HCV will defer treatment until more effective and better-tolerated drugs become available. Such treatments may include the long-awaited HCV protease inhibitors. Unlike interferon and ribavirin, which act through general antiviral and immune-modulating pathways, this new wave of drugs specifically targets HCV. Like HIV protease inhibitors, the drugs attempt to block the HCV serine protease enzyme, which plays a crucial role in viral replication. "The concept of HCV serine protease inhibitors is very exciting," according to Johns Hopkins' Sulkowski.

Boehringer Ingelheim developed the first HCV protease inhibitor to enter human studies, BILN 2061, and reported that a two-day course of treatment could reduce HCV viral loads by 100- to 1,000-fold. The company has reportedly halted development of this drug because of toxicities observed at high doses in animals, but other compounds are entering clinical tri-

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120 Wall Street, 13th Floor
New York, NY 10005-3908
Tel: 212-806-1600 • Fax 212-806-1601
reporters@amfar.org

als. Schering-Plough has an HCV protease inhibitor entering human studies, and Vertex Pharmaceuticals will begin phase I studies of its protease inhibitor, VX-950, in early 2004. Other compounds discussed at the AASLD meeting target other aspects of HCV replication.

At least initially, the new drugs will most likely be added to interferon and ribavirin, since researchers expect that HCV would quickly become resistant to a protease inhibitor used by itself. Even under the most optimistic projections, these new treatments will not be available in the clinic until 2007 at the earliest. For now, researchers continue to work on optimizing treatment outcomes and managing toxicities, while people with chronic HCV face difficult treatment decisions.