

HCV/HIV Today

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Opportunistic Infection Strategy

The human immunodeficiency virus (HIV) infects immune cells, impairing their function and eventually destroying cells over time. This gradually weakens the immune system and the body loses the ability to fight disease. While HIV is the culprit, most people who die of AIDS do not die of HIV, per se, but from the numerous infections that the body can no longer control due to the collapse of the immune system. Relatively common infections, which may cause little or no harm in a healthy person, take the opportunity provided by weakened immune defenses to cause disease. This is why they are called opportunistic infections (OIs).

A strategy to deal with OIs is an important part of a comprehensive, long-term strategy for managing HIV. The basics of an OI strategy include:

- Understanding what an OI is,
- Preventing infections by organisms that cause OIs,
- Using appropriate preventive treatment (sometimes called prophylaxis) against OIs,
- Treating infections as they occur and using appropriate maintenance therapy to prevent recurrence of OIs.

What is an Opportunistic Infection?

As noted above, an opportunistic infection is any infection or condition that takes the opportunity of a weakened immune system to cause disease. The Center for Disease Control (CDC) has developed a list of serious and life-threatening diseases, listed in a chart (not included), that in the presence of HIV infection are called Acquired Immune Deficiency Syndrome (AIDS)-defining OIs. In the presence of HIV infection, any one of these conditions results in a diagnosis of AIDS. Measures of immune health suggesting that a person is at serious risk for developing life-threatening conditions (i.e. when CD4+ cell counts are below 200 or CD4 percentages less than 14%), in the presence of HIV infection, also results in an AIDS diagnosis.

OIs can be relatively common infections, such as genital herpes. Not everyone with HIV who is having a herpes outbreak is deemed to have AIDS, however. To the contrary, herpes is deemed an opportunistic infection when it takes advantage of a severely weakened immune state to become more aggressive, persistent and less responsive to treatment.

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Therefore, having HIV and genital herpes isn't automatically considered AIDS, but having HIV and a herpes outbreak that persists for a month despite treatment is considered AIDS.

While there is a discrete list of AIDS-defining OIs, it's important to note that virtually any condition or disease can become opportunistic in the face of a weakened immune system. People living with HIV are not the only people at risk for OIs. Anyone with a severely weakened immune system, regardless of the cause, is at risk for OIs. For an OI to be the cause for an AIDS diagnosis, however, it must be one of the CDC AIDS-defining diseases occurring in the presence of HIV infection. People with HIV can get any number of worsening conditions that behave opportunistically and not all are on the CDC's list. Occasionally the CDC revisits this list, and over the years there have been several expansions. It's still possible, however, for people with HIV to develop opportunistic infections that are not on that list. Hepatitis C-associated disease is not AIDS-defining, though increasingly data show that people with HIV are at higher risk for more aggressive HCV-related liver disease. Most importantly virtually any condition or disease can behave in an opportunistic manner and the first line of defense is prevention.

Preventing Infections in the First Place

OIs are often caused by infections and some of them are preventable. For people never exposed to herpes, for example, practicing safer sex reduces the risk of genital herpes infection. If you are not infected with herpes simplex virus, there is no worry of herpes becoming opportunistic or life threatening. Project Inform has a publication called *Sex and Prevention Concerns for Positive People*. This publication contains information on how you can prevent infections by many of the organisms that can cause opportunistic infections. Some of these are sexually transmitted, and you can reduce your risk of infection by practicing safer sex. Others are preventable with vaccines. Still others can be avoided through safer food handling and preparation and/or by being aware of and avoiding (when possible) disease-causing organisms. This might include being aware of diseases that birds carry and not handling

birds, even those kept as pets. It may also include using gloves when changing cat litter boxes, or even better, having someone else deal with the cat litter box and/or keeping only indoor cats.

Recently there have been outbreaks of drug-resistant staph skin infections. The infection can be spread through casual contact, and some speculate that in urban areas staph infections may be spread through something as simple as sharing equipment at the gym. Because the organisms are drug resistant, treatment might require intravenous therapy. Doing something as simple as putting a towel down on shared gym equipment before use, and not using that towel to wipe sweat from your body, might help to prevent staph infection.

Preventing exposure to organisms is a great way to reduce your risk of particular OIs. In some cases, however, the organisms that can cause OIs are in our environment, unavoidable and/or exposures may have already occurred. People living with HIV should receive screening for many OIs upon first finding out that they are HIV-positive, as part of early lab screenings. This allows people to know, in some instances, if they are already exposed to an organism and enables people to learn about prevention for infections they don't already have. For more information on what's generally looked for on these lab tests, call the Project Inform hotline. In the case of *Pneumocystis carinii* pneumonia (PCP), however, it's simply not known how the organism is spread and it is assumed that most people are infected with it. In that case, preventive treatment is routinely used as the immune system weakens and the risk for PCP increases. PCP remains the leading cause of death of people with AIDS in the United States and is largely preventable.

Preventive Treatment for OIs

OIs are generally not a problem for people whose CD4+ cell counts remain stable above 200. It is extremely rare for a person living with HIV to die of AIDS when CD4+ cell counts are above 200. As CD4+ cell counts decline, however, a person's risk

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HIV and Personal Finance

By Per Larson

In the early 1990s, HIV was seen as a one-way street to all the “d-words” – disease, disability, and death. This emboldened viatical settlement companies to buy life insurance policies from people with HIV at prices near 90 percent of their face value. Low t-cells alone assured social security disability approval. People bought credit card, life and disability insurance, often running their credit up. Investment was shunned or used like a last-chance game of chance. The will became the legal document of the day in order to safeguard interests after death.

In the new millennium, however, HIV has become a two-way street. Disability can now be a time-out, a refuge from downsizing companies, a chance to reskill and redirect one’s life. Viatical settlement has been shoved aside by accelerated payouts of life benefits. Disability is still granted but often on the basis of medication side effects and the depression that can accompany long-term survival. Bankruptcy laws are being tightened. Investment and retirement are new concerns. And the legal document of the day is the living trust in order to safeguard interests during life.

All these shifts have left people with HIV with many left-over, no-longer-relevant and possibly dangerous ideas about personal finances. That’s on top of widely published advice in money magazines that is downright misleading when HIV is in the picture. Let’s pick our way among the land mines and opportunities generated by all this.

Dwindling Medical Insurance

The HMO-ization of America is now complete. I was trained as a HMO director at the Wharton School in an experimental program sponsored by the Robert Wood Johnson Foundation in 1976. I saw then what we experience now: the only way to cut costs is to cut service and pass on costs to consumers.

New York state has the best insurance laws in the US, laws so consumer protective that many insurers set up one company for the other 49 states and may refuse to even practice in NYS. These legal protections have spawned efforts by insurers to recoup their resulting high costs. Co-payments have skyrocketed, especially for the brand-name drugs HIV requires.

In the ‘90s, I advised that in these times the benefits tail must wag the employment dog: secure benefits may be more important than high salary or satisfying jobs. Employers are going bankrupt. Singles are be-

ing targeted in employer downsizings. AIDS Drug Assistance Plans (ADAPs) are in retrenchment. HIV medical practices are closing down and out-of-pocket costs for treatment are rising. Dollar maximums on medical policies converted from COBRA coverage are being hit.

Retiree benefits are under attack. This hits people on Medicare because of disability hard because once on Medicare you cannot purchase individual medical insurance. This can force people to impoverish themselves to qualify for Medicaid, adding financial insult to medical injury.

For people with HIV in New York and New Jersey there are three key protections: individual insurance is priced the same for everyone (community rating); continuity of coverage enables (non-Medicare eligible) people to go from one health plan to another; and people can keep individual medical insurance in force to pay for pharmaceuticals even when going onto Medicare because of disability.

Preserving private medical insurance benefits is key to preserving financial security. The ADAP Plus Insurance Continuation (APIC) program pays insurance premiums for those with incomes up to \$44,500/year and assets under \$25,000. In addition the AIDS Housing and Information Project (AHIP) has a lower income limit of under about \$15,000 a year and it has no asset limit. Get on these programs now to be “grandfathered” (i.e., remain included) later when the real crunch comes!

When major illness strikes, medical insurance become the greatest asset; worth far more than a condominium, investment portfolio or 401(k) retirement fund. Medical insurance is not a place to skimp. Especially with low income and assets, the best medical coverage is needed to withstand the onslaught of non-reimbursed expenses and payment delays.

With long-term survivorship many NY area people with HIV are tempted to become snowbirds and move to warmer climes. This can prompt individual insurers to cancel coverage, since in the past ten years medical insurance has become geographically bound. Insurers would like nothing better than to cancel coverage for moving out of this geographic area. If a person is on Medicare because of disability, the situation is worse since you cannot buy individual medical

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HIV and Personal Finance (continued)

insurance once you are Medicare eligible, which is 29 months after social security disability income payments start.

Unraveling Safety Net

The worst advice ever given to anyone with HIV in New York is to give away assets to go onto Medicaid. A bad economy and conservative administration have combined to cut Medicaid funding, tighten eligibility, and restrict federally mandated benefits. The social safety net is full of holes.

The administration has even cut back that hitherto sacred cow, Veterans' Administration (VA) benefits. On January 17, 2003, the feds suspended further enrollment of non-service-connected veterans with income over the levels used by the Department of Housing and Urban Development as the upper limits for housing assistance eligibility. This was justified because VA health enrollment has nearly tripled in recent years as veterans grew older and learned of the VA's prescription drug coverage.

However, if you have a low income and had military service, you may be eligible; if so, you should apply immediately. This is especially true if you anticipate your income may rise in the future. Many government programs have a tradition of grandfathering in people who had enrolled but whose circumstances improve later.

The funneling of federal funds into Pentagon budgets, the aging of our population, and the shift of baby boomers from funding public benefits to receiving them all are shredding society's safety net.

Other illness groups are learning how people with HIV managed to gain federal priorities in funding, and they are now competing fiercely for fewer dollars. The rise of faith-based social services and the rise in power of proponents of small government in policy-making positions makes the prospects for the safety net very poor.

Threatened Disability Benefits

Disability benefits are threatened not because people are more able to work, but because insurers had expected people with HIV to die and are now squeezed financially from many factors. Insurers with already bad investment records have been devastated by stock market losses where 95% of all stocks have fallen. Disability insurers have also collapsed because of terrible underwriting decisions in the '80s resulting in many claims from high-income doctors and lawyers. People with HIV have now been experiencing the sud-

den cancellation of benefits, offers of piddling buyouts, and reviews of doctor records for evidence that the patient stated that he or she "feels good."

Lastly, many policies from the '80s were tacitly designed to be underwritten (screened) at the time of a claim and not at the time the policy was written. These are claim disasters waiting to happen. The distinction is important. If insurers are after people with HIV because they think they're cured, that may be a losing battle. If insurers are trying to reduce claims, it means those who take the proper measures to defend their claims may be able to defend them.

Since the early '90s the only way to get disability coverage is through employment. The good news is that insurers have introduced "portable" coverage in the NY metro area, especially among financial institutions. This is insurance that you can convert to individual coverage without medical underwriting if you're terminated. It's a bit expensive, and deducts what Social Security would pay, but it's better than nothing.

The truth is that despite Social Security's publicized "Ticket To Work" program there has been no change in Social Security Disability (SSD) criteria for disability with HIV. That would require hearings just as it did in the early '90s.

Survivorship has re-introduced long-term dimensions into the financial decisions of people with HIV. With disability, time is the great eroder of income and assets. People on disability only get cost of living (COL) increases on the Social Security part of their income. If half your income gets no COL over ten years, that income has less purchasing power.

People on disability theoretically have far more time than working stiffs to upgrade skills, especially since programs like the New York State Vocational and Educational Services for Individuals with Disabilities (VESID) Program are more than ready to pay for even multiple training programs. But in practice this takes enormous self-motivation, which can be compromised by HIV's fatigue and unpredictability.

Today's work world is increasingly technological, and technology is evolving ever more rapidly. A disability time-out may work to recoup health, rebuild skills, and redirect life. Many have discovered new avocations far more satisfying than salary-focused vocations. But long-term disability can become equated with becoming obsolete in the work force and becoming sidelined in work-obsessed America.

Many who sold life insurance counted on the stock market to carry them forward. The market's betrayal of everyone has hurt those on disability far worse since they do not have good work prospects to rebuild those lost assets.

They may not have the same timeframes to weather the storm until things rebound.

Just about the time it was clear that new treatments were restoring longer life expectancies, leading people with HIV to think about longer-term investments such as having a home, the market crashed and money has rushed into real estate, inflating prices. Buying-in now would be risky.

When illness results in a fall from one's previous place in society, the adjustment is fraught with peril. When this happens in a culture that prizes work and money above all else, people on disability are doubly disadvantaged.

Unpreparedness for Senior Years

Near-normal life expectancies among people with HIV mean that aging is again the enemy. Yet people with HIV on disability left work with their financial foundations incomplete. Even if they had surplus income, people on disability can't save for the future tax-free. The new Bush savings plans, unlike the old Roth IRAs, can be funded with unearned disability income. While these savings may grow tax-free, they're a far cry from pensions and tax-deferred income plans where employers match their funds.

Retirement is the gaping hole now facing people with HIV. Disability incomes stop at age 65. Even social security payments may be lower for people with HIV due to underfunding. The senior years trigger the necessity to plan for long-term care, but people with HIV cannot get long-term care insurance. Even if they could, the premiums are very high and the coverage unregulated. But having HIV increases the likelihood that the illnesses of later years may occur earlier and harder.

The New Basis for Disability

The basis of going on disability has shifted from lab measures and opportunistic infections to medication side effects and long-term HIV-related conditions, including: hepatitis C and the harsh side effects of its treatment; possible medication-related stroke and heart conditions; and HIV-related depression. Especially with good long-term prospects, the idea of a disability timeout may be a good short or medium-term solution. This is especially true where side effects or symptoms may have resulted in poor performance in a company that's about to downsize, be merged, or go bankrupt. Disability benefits are a good life raft to reach a new safe work haven.

New Cash From Life Insurance

The sale of life insurance has been replaced by the acceleration of life insurance. Simply put, HIV sales dominated the viatical market during its many scandals.

Many investors got burned. Most of those investors today won't even deal with a company that sells policies from people with HIV. The entire industry fled HIV to buy policies from seniors. They even changed the very name of the process to "Life Settlement." Yet viaticalators have not yet caught on that going from 2-to-4 year life expectancies among people with AIDS to 8-to-12 year limits among seniors is even more risky and subject to abuse. When it does, people with HIV may be back in vogue, since they're easier to market to.

While some brokers still advertise, sellers need to be aware that illegal practices still abound and a seller may become embroiled in an investigation. In particular, anyone who obtained a policy by lying on an application should be aware that buyers are obligated in many states to report that to the law.

Fortunately, there is an alternative. Many group policies now carry a Living Benefits or Accelerated Death Benefits (ADB) clause. This permits a person with advanced HIV to apply for a payout of the death benefit. Insurers seem motivated to do this, since insurance sales are down and an ADB is a sales plus. Offering and granting ADBs for them demonstrates to clients that they are an alternative to viatical settlement. Insurers hate viaticals if only because they never let policies lapse, whereas the average policy lapses in just seven years. All that's required on many applications is a doctor's signature. Many insurers check only that and don't do medical reviews.

With long-term neurological impacts HIV is ever more a disease of competency. With financial support coming from a delicately organized network of sources, it's important to maintain clear lines of control. It's also important to arrange powers of attorney to provide for situations where help is needed to write checks, deal with authorities, or ensure premiums are paid.

For unmarrieds or people with complex family relationships, a will can be inadequate, leading to probate delays and nightmares. Yet, with longer life expectancies, people with HIV may put off even will making. One reason may be because wills aren't very useful to us while we're alive.

Those concerned about maintaining quality of life should consider not only powers of attorney but a living trust as a means to provide seamless means of control that will handle all the kinds of situations that can crop up with serious illness.

A trust provides instructions and control if families contest competency. It may help protect against family will contests. It guarantees that someone competent of

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your own choosing is always in control, and may minimize the delays and fees of probate. Beware the cheap will! It may camouflage a lawyer looking to handle a fee-lucrative estate.

New Opportunities in Entrepreneurship

Longer-term prospect make possible the many years needed to build the skills and experience for one's own business and then make it successful. Not everyone is suited for such self-discipline and sacrifice, and the failure rate of small businesses is high. But a niche business well suited to one's experience skills, and passion ranks right up there among life's securities and pleasures. This is especially true in today's corporatized, de-humanized jobs.

When you have many clients, you can be fired by one and yet survive and even thrive. Having seen how frail life is, the risks of entrepreneurship may pale by comparison. Motivation and focused desire are key to success, and these are also a natural by-product of fighting serious illness. It's important not to thwart these desires but to re-schedule and perhaps re-channel them. This may, in fact, be a good time to take an inventory of your interests through testing and profiling then using the results to re-prioritize and plan.

New Ways to Return to Work

Sometimes, the biggest problem is leaving the hard-won security of disability and public benefits for the uncertainty surrounding work today. Most disability policies will put people back on claim within six months of going back to work, but new workplace coverage may not take effect until twelve months on the job.

People who've run the HIV gauntlet may not be satisfied with just a job. When you've looked death in the eye, you may want the meaning or enjoyment of a career. You may need a job with flexibility and security that can tolerate the ups and downs of this disease. Yet, getting a job in today's post-dot-com world is tough even with perfect health. Consider the following:

- The world of work has radically changed and the degree of change is increasing.
- Unemployment is up, companies are cutting back, downsizing has become fashionable.
- Youth are seen as cheap to hire and easily managed, adaptable, with recent skills.
- Long-term survivorship may be accompanied by deterioration of skills and assets.

Returning to work is too complicated a subject to cover here. However, my previous series of articles for *Body Positive* on returning to work shows how to assess what benefit protections are absolutely needed and where risks can be taken. The series helps readers weigh factors such as drug resistance, treatment trends, and unpredictability of symptom outbreaks. It also outlines how to get funding for re-skilling, how to determine new career directions, and how to tradeoff and balance work wants with medical needs. It spells out how to use networking, rewrite resumes, and re-search industry opportunities.

Lastly, it deals with resume gaps, invasive interview questions, legal protections, and practical tactics for getting a job interview and offer and for settling safely into a new job.

Benefits obtained through work are key; benefits at the outset may in fact be more important than salary. Ten years ago it was key to get a job with benefits to make a disability timeout possible to build a life dream. Today a job may be key to generating the experience and skills necessary to make that life dream a reality.

Postscript: Financial Advice Must Adapt

As long as a decade ago, I was cautioning that many financial planning tools were inappropriate for people dealing with serious illness. For starters, 90 percent of financial planners may have a conflict of interest if they get their income by putting people into commission-generating investments or push their brokerage's own funds. People with HIV may need to protect capital, not gamble on stocks. They may need non-profit mutual fund families like Vanguard and TIAA-CREF rather than brokers.

HIV in the '90s dictated a focus on how to get people with disability successfully, get cash by selling life insurance, solve cash and debt problems, and postpone tax claims. In the 90s I had to change the way financial advice was delivered. I minimized meetings because they were expensive and draining. I found that people prefer to telecommute and handle questions singly by phone. I saw that bound financial plans produced by computers using general rules and assuming good health were worse than useless. I realized that employment benefits often turned out to be more important than assts such as investments and real estate.

In the new millennium all these changes continue to be relevant. But now we need to focus on career – our money machine – in order to stop the drain of inflation. We have to apply for grants to get new skills for possible new jobs. We have to fight dirty insurer practices to keep claims secure. We have to train doctors to understand the impact of their statements on disability deter-

minations. We need to tap lawyers specialized in relationship agreements, apartment law, and trusts.

I've had to retool as a financial advisor and advocate for people with HIV over the last ten years because people with HIV now have new concerns and challenges. Make sure your advisors and helpers have changed with the times as well.

Re-educate yourself financially. Beware generalized pop money magazine advice. Start with a unique inventory of where you are now: your advantages and your problems. Insist that whoever you work with or rely on for advice apply guidelines geared to your unique situation. This area is complicated. But the key areas are few in number. And it's well worth the trouble.

Author of the book Gay Money and over 125 articles, Per Larson has advised more than 800 people in the last ten years on financial implications of serious illness. Readers can consult Per's older articles on his Website Gay-Money.com or contact him at PerLarson@aol.com.

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Financial Dangers and Opportunities for People Living with HIV

The Dangers:

- *Medical Insurance Dwindling.* Medical insurance has become an even greater medical asset but one of dwindling value.
- *Safety Net Unraveling.* The safety net now suffocates; public and VA benefits are under attack.
- *Disability Benefits Threatened.* Squeezed dis-

ability insurers are squeezing insureds.

- *Skill & Asset Deterioration.* Heightened change and competition and increased fluctuation and unpredictability devalues previous experience and investment.
- *Senior Unpreparedness.* Age has resumed its traditional role as the enemy, finding people with HIV ill-equipped for retirement and long-term care.

The Opportunities:

- *New Basis for Disability.* The basis of going on disability has shifted to medication side effects and HIV-related conditions such as hepatitis C, cardiovascular conditions, and depression.
- *New Cash from Life Insurance.* The sale of life insurance has been replaced by the acceleration of life insurance.
- *Relationship-based Benefits.* Security is being sought in relationship-based benefits ranging from real estate to domestic partner insurance.
- *Entrepreneurship Opportunities.* Self-employment now competes with employment as the best source of benefits.
- *Return-to-Work (RTW) Possibilities.* RTW is possible in theory but difficult in practice.

All these changes testify to personal finance stability and/or prosperity as a major treatment tool. As treatment options multiply, paying for them becomes key. Group and private insurance remain key in not adding financial insult to injury and illness. Now that physical survival has become a reality, financial survival has become the next frontier.



HCV/HIV Bites

Editor's Note: *The following two articles deal with similar information, but different perspectives on it. The articles are presented without additional comment from HCV/HIV Today.*

People with HepC and HIV Have Best Chance of HCV Cure-Study

SYDNEY, Feb 16, AAP – People who suffer from hepatitis C (HCV) as well as HIV now have the highest ever chance of a HCV cure through a new generation combination therapy, according to a new study.

The study, presented at a scientific meeting in San Francisco last week, is good news for the 10% of HIV-infected people in Australia who also suffer from HCV.

Called AIDS Pegasys Ribavirin International Co-Infection Trial, or APRICOT, the study evaluated the safety and effectiveness of pegylated interferon combination therapy in people co-infected with HIV and HCV.

The study involved 868 people suffering from both HIV and HCV from 19 countries, including Australia.

HIV co-infection aggravates and accelerates the progression of liver disease in patients with HCV, resulting in a more rapid progression to cirrhosis and end-stage liver disease, according to the study authors.

As improvements in antiretroviral therapy have prolonged life expectancy of patients with HIV, liver disease has emerged as the leading cause of hospital admissions, morbidity and mortality for HIV patients co-infected with HCV.

The study found a combination therapy using the drugs Pegasys and Ribavirin achieved a record 40% cure rate for co-infected patients, compared to 12% with conventional therapy.

Both the Australian HCV Council and the Australian Society for HIV Medicine welcomed the findings.

"The results confirm that the new combination treatment should significantly help curb the long-term effect of HIV and HCV (which are) both serious public health issues," Jack Wallace of the Australian Hepatitis C Council said.

Levinia Crooks of the Australian Society for HIV Medicine said the results from the study enabled people

with HIV to undertake treatment for their HCV with the confidence that it would not effect their HIV treatment. AAP NEWSFEED, Feb. 16, 2004

HIV Coinfection Does Not Alter Efficacy of Hepatitis C Treatment

Coinfection with HIV does not significantly alter treatment responses in hepatitis C patients.

In a recent study, scientists in the United States examined HCV and HIV dynamics "in 10 coinfecting subjects in a trial of pegylated interferon-alpha2a (PEG-IFN) alone or combined with ribavirin (RBV), compared with IFN plus RBV for the treatment of HCV."

"Five subjects, four of whom were treated with PEG-IFN, achieved a sustained virological response, although it was delayed by greater than or equal to 1 week in three subjects," reported F.J. Torriani and coauthors at the University of California-San Diego.

"The median treatment efficacy in blocking virion production was 99.7% in the PEG-IFN group and 60% with standard IFN. In two patients with detectable HIV loads before starting HCV study drugs, we observed a 1-log decrease in HIV RNA load," published data indicated.

"The estimated HCV virion half-life was longer in the HIV-coinfected subjects, which suggests that coinfection may contribute to a slower clearance of HCV," the researchers concluded. "Although the early viral kinetics of coinfecting subjects treated with PEG-IFN or IFN differ from those of singly infected subjects, the treatment response seems unaffected."

Torriani and colleagues published their study in the Journal of Infectious Diseases (Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics during HCV treatment in HCV/HIV coinfection. J Infect Dis, 2003;188(10):1498-1507).

For additional information, contact F.J. Torriani, University of California at San Diego, Antiviral Research Center, Department of Medicine, Division of Infectious Diseases, 150 W. Washington St., Ste. 100, San Diego, CA 92103, USA.

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Impact of HCV Coinfection on Risk of HAART-Induced Liver Damage Reviewed

The impact of HCV infection on the risk of HAART-induced liver damage has been reviewed.

“Drug-induced liver injury (DILI) is the elevation of liver enzyme and/or bilirubin levels caused by the use of medication or drug,” scientists in the United States explained. In HIV patients, however, “some of these events may not be directly caused by medication. Acute viral hepatitis, reactivation of hepatitis B virus or hepatitis C virus (HCV) infection, and/or alcohol use may play roles.” “Elevated transaminase levels are a signal of liver injury, but most cases improve despite continuation of drug therapy,” noted M. Bonacini and colleagues working at the California Pacific Medical Center. “Approximately 33% of patients with HIV infection are coinfecting with HCV.”

“Patients with HIV or HCV infection are more prone to DILI, possibly because of impaired hepatocyte defense mechanisms,” published data indicated. “HCV coinfection is associated with a 2-10-fold chance of developing elevated transaminase levels during highly active antiretroviral therapy (HAART).”

Despite this added risk, “patients with HIV/HCV coinfection should not be denied HAART. Instead, they should be followed-up with monthly liver function tests and referred to specialists if grade 3-4 liver enzyme elevations occur,” the researchers concluded.

Bonacini and coauthors published their study in *Clinical Infectious Diseases* (Liver injury during highly active antiretroviral therapy: The effect of hepatitis C coinfection. *Clin Infect Dis*, 2004;38(Suppl. 2):S104-S108).

For more additional information contact M. Bonacini, California Pacific Medical Center, Dept. of Transplantation, San Francisco, CA 94114, USA.

The publisher of the journal *Clinical Infectious Diseases* can be contacted at: University of Chicago Press, 1427 E. 60th St., Chicago, IL 60637-2954, USA.

The information in this article comes under the major subject areas of Adverse Drug Effects, AIDS & HIV, Anti-Infectives, Gastroenterology, Hepatitis C, Hepatology, Infectious Disease and Virology.

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Clinical Trial of ANA971 Initiated

Anadys Pharmaceuticals, Inc., has initiated a clinical trial of ANA971, an orally administered prodrug of isatoribine.

Isatoribine is a nucleoside analog in development for the treatment of chronic hepatitis C virus (HCV) infection. To date, isatoribine has been administered to 48 subjects, including 28 patients chronically infected with HCV. A recent clinical study showed that intravenous administration of isatoribine was well tolerated and safe at all doses tested. Interim results from that study have also shown preliminary biological activity and viral load reduction in the patient populations whose clinical data has been completed and analyzed. ANA971, which was discovered by Anadys, is a prodrug designed to improve the oral bioavailability of isatoribine. Anadys has exclusive rights to market and commercialize isatoribine and ANA971 worldwide.

In preclinical animal studies, oral administration of ANA971 resulted in higher levels of isatoribine in the blood than were present after oral administration of isatoribine itself. The objectives of this clinical trial are to assess safety and pharmacokinetics in healthy volunteers following oral administration of ANA971.

“Initiation of this clinical trial represents another important step toward our goal of improvement of HCV patient care, and builds on the results of clinical work we have conducted with isatoribine,” said Devron Averett, PhD, senior VP of drug development for Anadys.

Isatoribine is a nucleoside analog Anadys is evaluating in ongoing clinical trials for the treatment of HCV infections. Isatoribine represents one of a new class of drugs being developed by Anadys to regulate innate immunity, combat HCV infection, and overcome

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limitations of current anti-HCV therapies. Anadys believes isatoribine interacts with a specific receptor, Toll-like receptor 7, or TLR7, that is present on certain immune system cells.

Although results of initial clinical trials may not be predictive of future results, interim results of the phase IB clinical trial show that isatoribine is biologically active in adults with chronic HCV infection and results from dosing a cohort of six HCV infected patients with 800mg of isatoribine showed a statistically significant reduction of viral load ($p=0.03$) at the end of 1 week, with a median change in viral load from baseline of $-0.94 \log_{10}$ units(a). Anadys is currently enrolling patients for an isatoribine phase I/II study.

HCV causes inflammation of the liver and degradation of liver function. HCV infection is currently the most common chronic blood-borne infection in the United States. Approximately 2.7 million people in the United States are chronically infected with HCV, and it causes 10,000 to 12,000 deaths a year in the United States. The U.S. Centers for Disease Control and Prevention, or CDC, estimates the annual mortality rate in the United States could increase to 38,000 by the year 2010, surpassing the number of deaths attributed annually to HIV/AIDS.

HCV is transmitted primarily through significant or repeated exposures to infected blood. Approximately two thirds of new infections progress to chronic infection. Chronic HCV infection may also progress to more serious complications such as cirrhosis of the liver, liver cancer, and death.

This article was prepared by Blood Weekly editors from staff and other reports. Copyright 2004, Blood Weekly via NewsRx.com & NewsRx.net.

EDITORS NOTE: *The related article, "Data reported from the phase IB trial of Isatoribine" was reprinted in the May issue of HCV/HIV Today.*

Hepatotoxic Effects Comparable for all ARVs

The drugs used to fight HIV infection all have comparable hepatotoxic effects.

HIV patients "frequently present with elevated levels of serum transaminases (alanine aminotransferase ALT and/or aspartate aminotransferase AST)," scientists in New York explained. "This has often been attributed to the hepatic effects of antiretroviral (ARV) drugs, including nonnucleoside reverse-transcriptase inhibitors (NNRTIs)." The results of "cohort studies investigating the incidence of hepatotoxicity among

patients receiving ARV therapy suggests that the overall rate of ALT and/or AST elevations is similar among all ARVs," according to D.T. Dieterich and colleagues at Mt. Sinai Medical Center.

"The rate of severe hepatotoxicity, ALT and/or AST levels >5 times the upper limit of normal (ULN) during therapy with NNRTIs is relatively low but may be significantly higher in patients with concurrent chronic viral hepatitis (hepatitis B or C)," published data indicated. "A comprehensive analysis of 17 randomized clinical trials of nevirapine demonstrated that 10% of all nevirapine-treated patients developed elevated levels of ALT and/or AST >5 times the ULN; however, almost two-thirds (6.3% of nevirapine-treated patients) of these elevations were asymptomatic."

"Symptomatic hepatic events were seen in 4.9% (3.2%-8.9%) of nevirapine-treated patients," the researchers noted in conclusion.

Dieterich and coauthors published their study in *Clinical Infectious Diseases* (Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*, 2004;38 (Suppl. 2):S80-S89).

For additional information, contact D.T. Dieterich, Mt. Sinai Medical Center, Department of Medicine, New York, NY 10029, USA.

Publisher contact information for the journal *Clinical Infectious Diseases* is: University of Chicago Press, 1427 E. 60th St., Chicago, IL 60637-2954, USA.

The information in this article comes under the major subject areas of Adverse Drug Effects, AIDS & HIV, Anti-Infectives, Hepatology and Virology.

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Company Announces U.S. Launch of Liver Fibrosis Assay HCV FibroSURE

Laboratory Corp. of America Holdings (LabCorp) (LH) announced the availability of HCV FibroSURE, a non-invasive blood test for assessing liver status in hepatitis C virus (HCV) patients.

Developed by leading hepatologists at the Pitie-Salpetriere Hospital and BioPredictive in France, HCV FibroSURE is only available in the U.S. through LabCorp.

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HCV/HIV Bites Continued

HCV FibroSURE provides an accessible alternative to liver biopsy, which physicians use to assess liver fibrosis and necroinflammatory activity in HCV patients. While liver biopsy has long been considered the gold standard to monitor the status of HCV and determine therapy options, it is an invasive procedure that carries a risk of serious complications. HCV FibroSURE uses a combination of six serum biochemical markers plus age and gender in a patented algorithm to determine the degree of liver fibrosis and the level of ongoing necroinflammatory activity. The test, which has been clinically available in Europe for the past 2 years, has been shown in several studies to enable quantitative, reproducible assessment of fibrogenic and necrotic activity in the liver of HCV patients. "The launch of this important new test once again validates LabCorp's strategy of creating a world-class national laboratory with the best and broadest array of diagnostic testing services," said Myla P. Lai-Goldman, MD, executive vice president, chief scientific officer and medical director at LabCorp. "Our focus on bringing forth innovative new technologies and tests, coupled with our scientific expertise and national scope, helps us broadly deliver vital new tools like BioPredictive's liver fibrosis assay to U.S. physicians managing HCV patients."

BioPredictive is currently researching clinical use of this test for other disease populations, including hepatitis B, HIV-HCV, and alcoholic and nonalcoholic steato hepatitis. "We anticipate that HCV FibroSURE will prove to be just the first in a family of innovative, noninvasive diagnostic testing products aimed at hepatitis and non-hepatitis-related conditions," said Dr. Thierry Poynard, head of hepatogastroenterology department in Pitie-Salpetriere Hospital in Paris, France, and researcher and founder of BioPredictive. "We look forward to continuing our relationship with LabCorp and building upon their expertise in the world of hepatitis testing for future products."

HCV FibroSURE is recommended for use to assess liver status following a diagnosis of HCV, as a baseline determination of liver status before initiating HCV therapy, as posttreatment assessment of liver status 6 months after therapy completion, and for noninvasive assessment of liver status in patients at risk of complications from a liver biopsy. According to the company, the blood sample for HCV FibroSURE can be collected in minutes and results can be returned to the physician within days. The test uses six biochemical markers that are routine and considered standard of care in the U.S.

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Hepatitis C Research Shared with Rivals *By Judy Silber*

In a move that could accelerate discovery of new hepatitis C (HCV) drugs, Chiron Corp. has decided to give competitors easier access to technology considered critical for work on the virus.

Until now, it's been difficult for smaller companies with limited resources to consider developing experimental drugs for HCV, a disease that affects about 3 million people in the U.S. and about 200 million people worldwide.

Chiron owns more than 100 patents related to the virus, yet until now charged expensive licensing fees when firms wanted to develop new drugs or diagnostic tests. The companies could not avoid a license, but many could not afford the fees.

With its new policy, the Emeryville-based company said it will waive an upfront fee, as well as payments related to the passage of time, charges that amount to several million dollars, according to a Chiron spokesman. Instead, firms will pay steeper royalty rates once their drugs receive approval from the U.S. Food and Drug Administration.

"We really are committed to innovation in this field, both our own and other companies," said John Gallagher, spokesman for Chiron. "We're willing to remove any perceived barriers that allows the innovation to get to market."

New drugs are needed for HCV because available drugs cause uncomfortable side effects and often aren't effective. If left untreated, the virus causes liver disease.

Some researchers say that Chiron's expensive licensing terms and aggressive defense of its patents have hindered progress in the HCV field. A 2003 report published by the National Academy of Sciences found the firm had filed seven lawsuits against companies for developing HCV drugs or diagnostic tests without a license. "(The fee) would and did stop us and has stopped many a firm," said Michael Farmer, chief operating officer for Prosetta Corp., a San Francisco biotechnology start-up company.

Prosetta had a promising technology with potential to treat HCV but steered clear of the virus because of Chiron's licensing fees, Farmer said. Instead, the company focused on HIV and other viruses where licenses weren't needed.

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This week, Prosetta became the first company to sign an agreement with Chiron under the new terms. The new license requires payments once Prosetta's drugs enter clinical trials and royalty fees once the FDA approves its treatments.

Gallagher insists Chiron is not caving into public pressure and has had a liberal licensing policy all along. Chiron has issued a total of 15 HCV licenses since 1987, when its researchers first identified the virus and sequenced its genetic code.

Chiron may have decided it would gain more by granting more licenses than restricting access, said Rick Kaufman, a patent attorney with Heller Ehrman White & McAuliffe LLP. This way, the company will potentially gain more revenue once the new drugs have received FDA approval, he said.

"I think it's an assessment they've made that this is the best way to address the market and also get the technology out there," Kaufman said.

Judy Silber covers biotechnology and the business of health care. Reach her at 925-977-8507.

Contra Costa Times (California) June, 2004

Immune Responses in Patients With Hepatitis C and HIV Described

Scientists describe virus dynamics and immune responses during treatment in patients co-infected with HCV and HIV.

According to a study from the U.S., "Mathematical modeling of the biological effect of interferon on virus decay permits the quantification of the efficacy (epsilon) of blocking virion production in different patient populations. The viral dynamic and immunologic responses of HCV infection to daily interferon therapy were characterized in 12 patients co-infected with human immunodeficiency virus (HIV). Three out of the 12 patients (25%) achieved an early viral response, a two-log reduction in HCV RNA by week 12.

"The mean epsilon of IFN-alpha in blocking HCV and HIV production were 72% and 74%, respectively," said Andrew H. Talal and colleagues at Cornell University. "For HCV epsilon was highest (97%) in the one patient who had a sustained viral response, while it was reduced in the other two patients (68% and 77%). Baseline HCV RNA and the number of CD3+CD56+16+ cells were inversely related ($r=0.89$, $p=0.03$), and baseline HCV-specific immune responses were significantly higher in the three patients with 2-log viral load reductions.

"These data suggest that: interferon efficacy at blocking virion production is correlated with treatment outcome in HIV/HCV co-infected patients; immunodeficient patients can respond to standard IFN-alpha; and both innate and adaptive immune responses may be important determinants of HCV RNA decline in response to interferon."

Talal and his coauthors published their study in *JAIDS – Journal of Acquired Immune Deficiency Syndromes* (Virus dynamics and immune responses during treatment in patients co-infected with hepatitis C and HIV. *JAIDS*, 2004;35(2):103-113).

For more information, contact Andrew H. Talal, Department of Medicine, Weill Medical College of Cornell University, 525 East 68th Street, A354, New York, NY 10021, USA.

Publisher contact information for the *JAIDS – Journal of Acquired Immune Deficiency Syndromes* is: Lippincott, Williams, and Wilkins, 530 Walnut Street, Philadelphia, PA 19106-3621, USA.

The information in this article comes under the major subject areas of Hepatitis C Therapy, AIDS and HIV Therapy, Hepatitis C Virus, Hepatology, Immunology, Immunotherapy, and Virology.

This article was prepared by Virus Weekly editor from staff and other reports. Copyright. June, 2004

Risk Factor Identified for Severe Liver Fibrosis

According to European researchers, severe liver fibrosis is frequently found in hepatitis C (HCV)-HIV coinfecting patients with elevated serum alanine aminotransferase (ALT) levels. The rate of complications due to end-stage liver disease is high in these patients, and anti-HCV therapy should be considered a priority, said the study, which was published in *Clinical Infectious Diseases*. The study was performed in 10 European healthcare centers with 914 coinfecting patients from 1992 to 2002.

Source: Health and Medicine Week.

Source: Company release.

www.hemophilia.org. April, 2004. Reprint permission granted with credit to NHF.

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New Phase II Trial Slated for Chronic Hepatitis C

Human Genome Sciences, Inc., (NASDAQ:HGSI) announced that it has begun dosing patients in a Phase II clinical trial of Albuferon (albumin-interferon alpha) in patients with chronic hepatitis C virus (HCV) who are naïve to interferon-alpha treatments.

The Phase II trial is randomized, open-label, multi-center study to evaluate the safety, tolerability, pharmacology, and optimal dosing of Albuferon. The Phase II clinical trial will be conducted in Canada, and will enroll approximately 40 patients with HCV genotype 1. Genotype 1 accounts for nearly 70% of all HCV infections in North America and is generally regarded as the most difficult HCV genotype to treat. A minimum of ten patients will be randomized to each of three dose groups, which will be given two doses of Albuferon administered subcutaneously 14 days apart. The pharmacodynamic activity of Albuferon will be evaluated based on HCV RNA viral load reductions over a 28-day period of exposure and early virologic response at day 28. One of the study objectives is to identify a range of active doses that Human Genome Sciences plans to evaluate in a larger 48-week study of Albuferon in combination with ribavirin in patients with HCV genotype 1 who are naïve to interferon treatment.

Interim results of an ongoing Phase I/II clinical trial of Albuferon in interferon-experienced adults with chronic hepatitis C were presented at the annual meeting of the European Association for the Study of the Liver. Interim results demonstrate that Albuferon is well tolerated, has a prolonged half-life, and is biologically active. On average, patients participating in the ongoing clinical trial had been treated previously for approximately 68 weeks with regimens containing interferon alpha or pegylated interferon. Data were presented at the EASL meeting on 51 patients who were enrolled under an amendment to the original protocol and were treated with single doses of Albuferon administered subcutaneously at 120 mcg, 180 mcg, 240 mcg, 320 mcg, 400 mcg, 500 mcg, or 600 mcg, or with 2 doses of Albuferon administered subcutaneously 14 days apart at 400 mcg or 500 mcg. All cohorts treated under the amended protocol showed evidence of biological activity. Viral load levels represent the quantity of HCV in the blood, and reductions in viral load are a surrogate marker for clinical benefit. Fifty-five percent of Albuferon-treated patients in the combined single-injection and double-injection cohorts experienced an antiviral response, as demonstrated by reductions in their viral load of 0.5 log or greater at two consecutive time points. Of those experiencing an antiviral response, 79% experienced reductions of at least 0.9 log units.

Vijayan Balan, M.D., a lead investigator and director of the Hepatobiliary Clinic, at the Mayo Clinic Hospital, said, "Hepatitis C is the most common chronic blood-borne infection in the developed world. It afflicts approximately four million people in the United States alone, about four times the number afflicted by HIV, the virus that causes AIDS. There is a significant need to provide hepatitis C patients with additional treatment options, and Albuferon has looked promising in our initial studies. Further development in interferon-naïve patients is warranted."

Albuferon is a novel, long-acting form of interferon alpha. Recombinant interferon-alpha is approved for the treatment of hepatitis C, hepatitis B, and a broad range of cancers. Human Genome Sciences modified interferon alpha to improve its pharmacological properties by using the company's proprietary albumin fusion technology. Human Genome Sciences is developing Albuferon for use in the treatment of chronic HCV.

This article was prepared by Drug Week editors from staff and other reports. Drug Week, June 2004

Vertex Pharmaceuticals Announces Initiation of First Human Clinical Trial for VX-950, an Investigational Oral Protease Inhibitor for the Treatment of Hepatitis C

Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) announced today the initiation of a Phase 1 clinical trial for VX-950, an investigational oral protease inhibitor for the treatment of hepatitis C virus (HCV) infection. The objective of this trial is to assess safety, tolerability and pharmacokinetics in escalating single doses of VX-950 in healthy volunteers. Approximately 35 healthy subjects will participate in the study, which is being conducted in Europe. Successful completion of the Phase 1 clinical trial will enable a first study of VX-950 in HCV-infected patients. Such a study is currently planned to start in the fourth quarter of 2004.

VX-950 is Vertex's lead oral HCV protease inhibitor and one of a new class of direct antivirals in development for the treatment of HCV. Preclinical studies have shown that VX-950 significantly reduces levels of HCV RNA in both an in vitro replicon system and infectious virus assays. At a scientific conference in October 2003, Vertex scientists reported that VX-950 reduced HCV RNA 10,000-fold (4 log₁₀) in nine days in an in vitro replicon assay. Preclinical pharmacokinetic studies have indicated that VX-950 is orally bioavailable and achieves excellent exposures in the liver, the target organ for HCV treatment. The initiation of clinical test-

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ing of VX-950 represents a first step towards establishing the safety and tolerability in humans.

“Preclinical data to date have indicated that direct antivirals such as VX-950 may represent a powerful new approach to the treatment of HCV infection,” stated John J. Alam, M.D., Senior Vice President of Drug Evaluation and Approval at Vertex. “Initiation of human clinical trials for VX-950 reflects Vertex’s commitment to leadership in the development and commercialization of novel antivirals for the treatment of HCV infection, and it is one of several important clinical milestones for Vertex’s proprietary development programs in 2004.”

Clinical Need and Market Opportunity in HCV Infection

Chronic hepatitis C virus (HCV) infection is a serious public health concern affecting approximately 2.7 million people in the U.S. HCV causes inflammation of the liver, which may lead to fibrosis and cirrhosis, liver cancer, and ultimately, liver failure. Cirrhosis of the liver resulting from chronic HCV infection is the leading indication for liver transplantation in the U.S. Due to the asymptomatic nature of HCV infection, it often goes undetected for up to 20 years following initial infection. Worldwide, the disease strikes as many as 185 million people each year, 8,000 to 10,000 people in the U.S. die from complications of HCV.

The current standard care of HCV treatment is a combination of weekly injections of pegylated interferon alpha (peg-IFN) and daily oral dosing of ribavirin. This combination therapy provides a sustained viral response for only 40 to 50 percent of patients chronically infected with genotype 1 HCV, the most difficult viral strain to treat and the most common form in the U.S.

Vertex’s drug development portfolio includes two different approaches for advancing the future standard-of-care in HCV. In addition to VX-950, Vertex is developing merimepodib, an IMPDH inhibitor in combination with pegylated interferon alpha (peg-IFN) and ribavirin. Addition of merimepodib to standard therapy has the potential to enhance antiviral activity and improve clinical outcomes for a larger percentage of patients. Vertex owns worldwide development and commercialization rights for both merimepodib and VX-950. *PR Newswire June, 2004 Editor’s Note: A previous article on VX-950 was published in HCV/HIV Today, Vol. 5, Issue 3, May 2004.*

Editor’s Note: The following information was provided by the HCV Advocate. The Paperback book with interactive CD-ROM was published in October 2003 and was listed by Amazon.com as selling for \$29.95.

Winning the Hepatitis C Battle

by Shekhar Challa, M.D.

Winning the Hepatitis C Battle is a helpful, in-depth book written by Shekhar Challa, M.D. Tapping into more than 13 years of experience working with hepatitis C patients, Dr. Challa wanted to communicate the necessary information in an easy-to-understand format. While the book covers the many technical topics needed to have a complete understanding of the disease, it includes the personal stories of many patients, helping those dealing with hepatitis C reach a greater understanding.

Chapter titles in the book are:

- * A Life-Changing Diagnosis
- * Where Hepatitis C Strikes: The Liver
- * What It Is: Hepatitis C
- * Signs, Symptoms and Complications of Hepatitis C
- * What To Do: Treatment
- * Herbs and Alternative Medicine
- * Frequently Asked Questions

Winning the Hepatitis C Battle offers numerous graphics, tables and aids for helping you understand this disease. The section “Live Easy with Side Effects” details information to help patients as they go through the difficult treatment process.

HCV Treatment for Nonresponders

Liz Highleyman

With recent improvements in therapy for hepatitis C, there is a growing interest in the management of patients who have not responded to previous treatment. Nonresponders are patients who do not achieve a sustained virological response (SVR) six months after the end of therapy. They fall into three groups: those who experience little or no decrease in HCV viral load (complete nonresponders); those who achieve a significant reduction in viral load at least 1-2 logs but do not clear the virus completely (partial responders); and those who achieve an early virological response (EVR) or end-of-treatment response (ETR) followed by a viral load rebound (relapsers). About half of patients with HCV genotype 1 receiving the current best treatment do not achieve an SVR.

Three basic retreatment strategies are being studied for nonresponders. The first involves administering the current standard of care, pegylated interferon plus ribavirin, to patients who previously received suboptimal therapy with standard interferon alone (monotherapy), standard interferon plus ribavirin, or pegylated interferon monotherapy. The second strategy is to administer pegylated interferon plus ribavirin at higher doses or for longer periods. The third involves treatment with new drugs instead of, or in addition to, pegylated interferon and ribavirin.

Current Standard of Care

Research indicates that about 20% of patients who did not respond to the older standard interferon can achieve an SVR with pegylated interferon plus ribavirin. For example, in the April 2004 issue of *Gastroenterology*, Mitchell Shiffman and colleagues reported the first results from the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial. The study evaluated 604 patients who did not respond to previous treatment with standard interferon, with or without ribavirin. Subjects were retreated with pegylated interferon (Pegasys) 180 µg per week plus ribavirin. Those who achieved an EVR (undetectable HCV viral load at 20 weeks) continued treatment for 48 weeks. At the end of treatment, 32% of patients had an undetectable viral load; at the end of follow-up (72 weeks), 18% achieved an SVR. Among those who achieved an EVR at 12 weeks, 34% went on to achieve an SVR, but only three patients (1%) who did not achieve an EVR later achieved an SVR. SVR rates were 14% for patients with HCV genotype 1, 65% for genotype 2, and 54% for genotype 3. African Americans and patients over age 60 had lower SVR rates. The researchers concluded

that "[s]elected nonresponders to previous interferon-based therapy can achieve SVR following retreatment with [Pegasys] and ribavirin."

The likelihood of successful retreatment is highest when patients who originally received standard interferon monotherapy are retreated with pegylated interferon plus ribavirin. It is uncommon for patients to respond to retreatment with the same suboptimal regimen. In both HALT-C and ACTG 5071 (a study of patients coinfecting with HCV and HIV), patients who started at lower doses of ribavirin in an effort to reduce toxicity were less likely to achieve an SVR, confirming that ribavirin helps prevent relapse.

It is also possible that individuals who did not respond well to Peg-Intron, the first approved pegylated interferon, may do better with Pegasys. At the May 2004 Digestive Disease Week (DDW) conference, N. Zeng and colleagues from Johns Hopkins reported on the use of Pegasys plus ribavirin in 15 genotype 1 patients who failed to respond to Peg-Intron plus ribavirin. At 24 weeks, 40% (six subjects) had undetectable HCV viral load. One-third of the continued nonresponders (3 out of 9) and just one of the responders were African American. SVR rates are not yet available, and patients will continue to be followed. A currently enrolling study called REPEAT will also look at retreatment with Pegasys plus ribavirin in Peg-Intron nonresponders. (For details and study sites, see www.clinicaltrials.gov/ct/gui/show/NCT00039871.)

Longer or Higher-Dose Therapy

The usual course of therapy for HCV is 48 weeks for patients with genotype 1 HCV and 24 weeks for those with genotypes 2 or 3. While most genotype 2 or 3 patients do well with a 24-week course, some studies suggest that 72 weeks may work better for those with genotype 1. This may be especially true for HCV/HIV coinfecting patients, who appear to respond more slowly to HCV therapy. The benefits of higher doses are less clear, however. C. Bapin reported at the April 2004 European Association for the Study of the Liver (EASL) conference that 24% of previous standard interferon monotherapy or standard interferon plus ribavirin nonresponders achieved a SVR after 48 weeks of retreatment with Peg-Intron plus ribavirin. However, subjects who started with an initial Peg-Intron dose of 2 µg/kg per week for the first 12 weeks did not respond better

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than those who received the usual 1.5 µg/kg per week dose for the entire 48 weeks.

Other Drugs

One therapy under study for treating nonresponders is consensus interferon-alpha (Infergen), a recombinant product that combines the features of several natural alpha interferons. At the recent DDW meeting, Steve Kaiser reported on a study of high-dose Infergen in previous nonresponders. In this study, 50 subjects (about half with genotype 1) who did not respond to pegylated interferon plus ribavirin were retreated with either 9 µg Infergen daily for 16 weeks or high-dose (27 µg) daily Infergen induction therapy for 4 weeks followed by 18 µg daily for 12 weeks. All patients then received continued therapy with 9 µg daily Infergen plus ribavirin for an additional 34-56 weeks. Twenty-four weeks into the combination therapy phase, 46% of subjects who started with 9 µg Infergen and 52% of those who started with 27 µg achieved an undetectable HCV viral load. ETR rates were 42% and 48%, respectively, and SVR rates were 23% and 27%. "[Consensus interferon] daily dosing/induction therapy together with subsequent [ribavirin] combination therapy thus shows sustained viral response rates in about one quarter of previous peginterferon combination therapy nonresponders," the researchers concluded.

Another drug being studied in nonresponders is interferon-gamma-1b (Actimmune), now in Phase II trials. In a pilot study presented at the DDW conference, Carroll Leevy reported that after 24 weeks, 47% of previous Peg-Intron plus ribavirin nonresponders achieved an undetectable HCV viral load when retreated with a combination of Infergen 15 µg daily plus Actimmune 50 µg twice weekly plus ribavirin. SVR results are not yet available, and the study is continuing. Although both Kaiser and Leevy reported that treatment was generally well-tolerated in their studies, some physicians are skeptical about using high daily doses of Infergen and/or Actimmune due to potential toxicity. Further research is needed to determine whether less frequent or lower doses would produce similar results.

Future Prospects

Failure to achieve a sustained virological response can be discouraging. But research indicates that patients may experience a histological response, improved liver tissue health, or a reduced rate of fibrosis progression even if they do not completely clear HCV.

This is most likely in partial responders who experience some decrease in viral load. Even in the absence of SVR, treatment may help prevent progression to decompensated cirrhosis and lower the risk of hepatocellular carcinoma (liver cancer). For this reason, some experts believe nonresponders may benefit from interferon maintenance therapy. Due to its toxicity, long-term therapy with full-dose interferon is an unattractive prospect. But even low-dose maintenance therapy may be useful. This is now being evaluated in a few large trials including HALT-C.

Given the side effects, inconvenience, and cost of HCV therapy, the decision whether to retreat can be difficult. The current National Institutes of Health (NIH) consensus guidelines recommend that retreatment should be considered especially for patients with advanced liver fibrosis or cirrhosis, who stand to benefit the most from therapy. Improvements in HCV therapy are rapidly emerging, and it is probable that future therapeutic advances including drugs from entirely new classes such as protease inhibitors will offer improved prospects for successful retreatment of patients who have not previously responded to therapy.

www.HCVadvocate.org. June 2004. Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.

What are STIs and What are the Goals of STIs?

STIs (Structured Treatment Interruptions) involve going off anti-HIV therapy for periods of time in a structured and strategic fashion, typically guided by increased lab and health monitoring. In all, more than two dozen studies of STIs of varying types have been conducted since 1998. It is important to note that interpreting the results of STI research can be challenging. Some of the assumptions about HIV disease that led researchers to investigate treatment interruptions in the first place have yet to be proven conclusively. At least some of the research on STIs, however, has been promising and other research has made clear those areas where interrupting therapy is neither safe nor effective.

The discussion that follows will explore what is known about the following STI-related strategies where the goals were:

- Interrupting anti-HIV therapy to reinvigorate the immune response,
- Interrupting anti-HIV therapy in people experiencing treatment fatigue,
- Interrupting anti-HIV therapy in people to reduce the costs and side effects of therapy, and
- Interrupting anti-HIV therapy before starting a third line or salvage therapy regimen.

Interrupting anti-HIV therapy to reinvigorate the immune response

The immune rationale for studies of STIs to reinvigorate immune responses came from observations suggesting that HIV disease progression might be linked to the loss of a specific type of immune cell, called an HIV-specific cytotoxic lymphocyte (CTL). HIV-specific CTLs are cells that seek out and destroy other HIV-infected cells. Some findings indicate that long-term non-progressors—those who remain well for many years despite HIV infection, without the use of anti-HIV therapy—manage to maintain potent HIV-specific CTLs while people who progress more rapidly do not. Not all research supports that the loss of HIV-specific CTLs is responsible for HIV disease progression. Nevertheless, a number of studies including treatment during acute infection followed by STIs or STIs combined with therapeutic vaccines to enhance immune responses against HIV, were planned or initiated.

The goal of this research is to enhance HIV-specific immune responses and thus improve the body's own ability to control HIV infection for the longer-term, pref-

erably without anti-HIV therapy. In this context, anti-HIV therapy (with or without the use of an experimental therapeutic vaccine against HIV) was used to curb the destruction of cells by HIV. By starting and stopping therapy periodically, it was hoped that with each successive treatment interruption the immune system would demonstrate increasing ability to control HIV on its own. This approach is sometimes called autoimmunization, where it's hoped that modulating a person's exposure to virus can induce a more potent and effective response against the virus.

Ultimately the goal of this approach is to enhance and preserve HIV-specific immune responses in people with very, very early HIV infection, such that a person's immune system would better control HIV on its own for longer, perhaps indefinitely, without anti-HIV therapy. Or, for people with established HIV infection, the goal is to enhance or restore HIV-specific immune responses, such that those who have lost these responses might regain them and thus hopefully do better in the long-term.

The results of this research, however, were exactly the opposite of what was expected. People who had been infected longest were actually the most likely to carry a broader and more potent HIV specific CTL response. Those who had initiated anti-HIV therapy during primary infection had a fairly narrow and weak CTL response that could be boosted somewhat during a treatment interruption, but then tapered again back to lower levels after reinitiating treatment. Similar results have been found in several other studies of STIs in people with chronic, established HIV infection.

More recently, several studies began to combine STIs with immune modulating therapies such as IL-2 (Interleukin-2) or therapeutic vaccines. The hope is that these therapies, used in conjunction with an STI may provide the additional lift necessary to orchestrate a stronger immune response to HIV. Although several studies are still ongoing, the results reported so far have not been promising. As such, people who are hoping to "boost" their immune response to HIV should not look to STIs as a proven course.

There are, however, data that show it may be safe for people who started anti-HIV therapy early to go off of treatment safely. Many people who initially went on anti-HIV therapy early now wish to try going without it. The decision to simply stop anti-HIV therapy and then reinitiate therapy according to current Federal Guidelines is not an STI, per se.

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STI's (continued)

There have, however, been STI studies conducted in people who initiated treatment in the "hit it hard, hit it early" era of treatment. People in this population have been among the most likely to be able to discontinue anti-HIV therapy. On average, roughly one third to one half of people treated early in HIV disease who have participated in STI research have been able to go off of treatment and stay off for months at a time without virus levels climbing again. Some were able to achieve virologic control during the first treatment interruption; others required two or three treatment interruptions. The results of STIs in people who initiated treatment somewhat later (six months to several years after primary infection) have been less promising and consistent. Generally, however, people whose viral load was low and whose CD4+ cell counts were high before starting anti-HIV therapy are also the most likely to achieve long-term suppression of virus following an interruption.

For individuals who were treated early in HIV disease and who wish to attempt going off HIV medications, there are indications that it may be possible to do so safely. As reported in studies, however, treatment interruptions carry the risk even in people treated during primary infection of leading to loss of control of the virus. There is no particular STI protocol in this population that can be recommended over another. People who wish to go off their medications, should only do so with the full knowledge and assistance of their doctors. It is important to monitor CD4+ cell counts and viral load following a treatment interruption and to resume anti-HIV therapy in accordance with the Federal Guidelines. Most doctors would recommend reinitiating anti-HIV therapy if CD4+ cells drop below 200 or viral load climbs and remains over 55,000. It is also important to remember that some people experience symptoms of acute infection in the first weeks following a treatment interruption. These symptoms are flu-like in nature and can include a fever, muscle aches, swollen lymph nodes, and a rash.

Interrupting anti-HIV therapy in people experiencing treatment fatigue

Treatment fatigue is when a person is simply "tired" of taking anti-HIV medicines. For people who wish to discontinue anti-HIV therapy due to treatment fatigue the data are somewhat conflicting. Perhaps the most

hopeful data to emerge from the various STI studies is that some people can successfully take a break from treatment without developing drug resistance, treatment failure or symptoms of HIV disease progression. Moreover, several factors have emerged that help predict when a person may have a poorer outcome during their time off of treatment. These are:

- a low CD4+ count (less than 200) prior to starting anti-HIV therapy
- a high viral load (greater than 55,000) prior to starting anti-HIV therapy
- poorer control of virus while on therapy or other signs of developing drug resistance
- a previous opportunistic infection

There is a significant difference between studies looking at a single treatment interruptions. There have been several studies that used CD4+ cell counts and viral load as a guide for when to restart therapy following a single treatment interruption. Nearly all of these studies were conducted in people who had achieved undetectable viral loads for at least the past twelve months and a CD4+ cell count above 350 for the past six months. In most studies, at least one third of volunteers were able to remain off of therapy for at least one year. The median time off therapy for the remainder of the study participants ranged from eight to twelve weeks.

It should be noted, however, that people who interrupted treatment had significant drops in their CD4+ cell counts (on average dropping 50%) compared to people who remained on treatment. Without appropriate preventive medicine against opportunistic infection, these CD4+ cell count decreases could be dangerous for people whose counts drop below 200 during an interruption. Also, the majority of the studies were unable to consistently measure significant or meaningful improvements in cholesterol and triglycerides in people taking an STI versus people on continuous therapy. Study dropout rates also tended to be higher among those taking STIs compared to those who received continuous therapy in most of these trials, indicating that treatment interruptions may actually be more difficult to manage than taking pills every day.

For people with treatment fatigue, who wish to take a break from anti-HIV therapy, there are certain guidelines that may be followed. Because of the risks for disease progression and opportunistic infections, careful monitoring by your doctor is critical. People should check their healthcare benefits (whether through private insurance or public assistance) to ensure that additional viral load and CD4+ cell counts

will be covered if needed. In situations where additional tests are not covered, it can be argued that the cost of additional tests will be far less than the costs associated with remaining on most anti-HIV therapy regimens.

A viral load test and CD4+ cell count should be taken before interrupting therapy and at least three months following the interruption. You and your doctor should decide in advance what factors will indicate that you should resume anti-HIV therapy. At minimum, most people would recommend using the Federal Guidelines for anti-HIV treatment (i.e. CD4+ cell counts that drop below 200 and/or a viral load count that settles above 55,000) as a basis for reinitiating therapy.

Your doctor may also wish to check your CD4+ cell count sooner if your counts were near 200 before stopping therapy, you had less than 200 cells before starting your last regimen or you have previously had an opportunistic infection. Federal Guidelines for preventing and treating opportunistic infections should absolutely be followed. Whenever CD4+ cell counts drop below 200, preventive treatment for opportunistic infections is highly recommended.

Interrupting anti-HIV therapy in people to reduce the costs and side effect of therapy

Another form of STIs studied were those designed primarily to reduce the amount of time a person spent on treatment. The first attempt, which directed volunteers to go on and off therapy every fourteen days, resulted in several people in the study developing drug-resistant virus and losing control of their viral load. Another small study of continuous cycles of seven days on and then seven days off therapy resulted in improvements in side effects and quality of life issues for people attempting STIs versus people on uninterrupted therapy. A larger study in the U.S. is ongoing. A similar study in Thailand had conflicting results, however, so it is impossible to state conclusively whether STIs of this type are likely to work.

Interrupting anti-HIV therapy before starting a third line regimen

When a person is attempting to construct a new regimen that may contain specific medications that had previously failed, the combination is often referred to as a third line or salvage regimen. Because salvage also means, "to save," others sometimes call salvage regimens, "rescue therapy". For the purposes of this article, the term *third line therapy* will be used to describe

a new regimen that typically contains four or more different anti-HIV drugs, some of which a person's virus may carry resistance for.

The theory behind treatment interruptions in settings where a person wishes to start a third line regimen is the hope that time spent off therapy may enhance the virus' susceptibility to treatments to which it had previously become resistant. Studies conducted in the early days of anti-HIV treatment found that when a person goes off a therapy to which the virus has become resistant, the newly emerging virus will rapidly revert to what is called wild-type. Wild-type virus is one of the many strains of HIV that exist in the bodies of people living with HIV. It is the strain of virus that reproduces most easily and is sensitive to anti-HIV therapy. The earlier studies found that when the wild-type virus takes over as the dominant form existing in the body, a therapy that had stopped working could sometimes regain some of its earlier potency.

For this reason, several studies have now been conducted examining the impact of treatment interruptions in third line settings. One study from Barcelona found that a three-month treatment interruption did not provide any additional advantages before starting a third line regimen compared to starting immediately. The GIGHAART study from France, which used a shorter interruption, did show that people taking a treatment interruption had larger reductions in virus when they started their next regimen than those who started their next regimen immediately. More recently, researchers in San Francisco conducted a similar study comparing a group of patients who were given a four-month treatment interruption before starting a salvage regimen to another group who started the new regimen immediately. Unfortunately there were no benefits in viral response to treatment in the group who underwent the treatment interruption. In fact, people who had interrupted treatment for four months were more likely than the other group to develop an opportunistic infection or die. Although the authors of this study concluded that treatment interruptions should not be attempted in people with lower CD4+ counts and drug-resistant virus, it may be fairer to say that they should certainly not be attempted in this population without proper medication and follow-up to prevent the development of opportunistic infections. It may also be that four months is too long to wait before resuming anti-HIV therapy.

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Opportunistic Infection Strategy (continued)

for developing opportunistic conditions increases. Perhaps the best strategy for preventing OIs is to not let CD4+ cell counts fall close to the 200 threshold. Therefore the Federal Guidelines for the use of anti-HIV therapy recommend that people consider starting anti-HIV therapy when CD4+ cell counts are 350 or below. Moreover the Guidelines strongly recommend treatment for anyone experiencing symptoms of HIV disease (regardless of CD4+ cell counts) and for anyone with CD4+ cell counts of 200 or below. This is because anti-HIV therapy has been shown to stop the destruction of immune cells by HIV, preventing the further decline in immune defenses.

There are Federal Guidelines for the prevention and treatment of HIV-related opportunistic infections. A summary of these guidelines is available in Project Inform's *Opportunistic Infections Chart*.

In general, if CD4+ cell counts fall to 200 or below (or CD4 percentage falls below 14), people are at increased risk for PCP and preventive therapy is indicated. For people experiencing other symptoms of HIV infection, particularly recurrent fungal (candida) infections, PCP preventive therapy is often initiated when CD4+ cell counts are higher, around 300. If CD4+ cell counts fall to between 150-100, preventive therapy for toxoplasmosis is recommended for people who are toxo-positive. If CD4+ cell counts fall to 50 or below, preventive therapy for MAC and CMV is recommended. For people who have suspected exposure to tuberculosis, preventive therapy is warranted.

Treating Infections as They Occur

As noted previously, Project Inform's *OI Chart* summarizes Federal Guidelines for the treatment of the major OIs. Because HIV replicates more when the immune system is actively battling an infection, treating infections as they occur is critical not only to dealing with the infection, but also curbing further destruction of the immune system by HIV. This is true whether or not the infection is an opportunistic infection. When it comes to OIs and many issues in later-stage HIV disease, diagnosing some infections can be difficult.

One of the biggest challenges of OI treatment is early diagnosis, before it has been able to take hold in many different organ systems (e.g. the lungs, colon, brain, bone marrow, etc.). The earlier something is diagnosed and treated, the more likely treatment will be successful and result in full recovery. This means regular monitoring by a doctor (at least quarterly) and talking to a doctor about symptoms. If you experience any new or unusual symptoms and are between doctor visits, make an appointment—don't wait for three

months to have something looked at. Keep a health journal or diary, or merely write on a calendar when a new or unusual symptom occurs and record how long the symptom remains. This might help a doctor figure out if a symptom is a drug side effect, sign of an OI or something else.

Many OIs have the same symptoms and some infections may be masking others—thus initial treatment may deal with part of a problem, but not the whole problem. Dealing successfully with multiple infections may take diligence and persistence when dealing with multiple doctors and specialists. It's ideal to have your primary doctor leading the charge, talking with all of your other doctors and specialists and making sure that they're talking to one another. The most difficult part of dealing with multiple conditions is that doctors often aren't very good about talking to each other. It easily can become a full time job trying to juggle doctor appointments and many different doctors ordering many different laboratory tests. It's your primary doctor's job to coordinate all of this, even when they're busy. Especially in cases where many problems may be rearing their heads at once, preparing for your appointments, writing down your questions beforehand and having an advocate with you to record answers to your questions is strongly encouraged.

Once a condition is diagnosed, following a course of recommended treatment through to completion is vital. Drugs to treat some opportunistic infections may interact with anti-HIV medications. Any time a new treatment is being added to your regimen an assessment should be done to make sure it's safe to use with the other medications you are taking and to make any necessary dose adjustments to compensate for drug interactions.

Maintenance Therapy

After treating an OI, sometimes life-long medications are required to prevent the recurrence of the disease. This is called maintenance therapy. In some instances maintenance therapy may be stopped if a person is able to see sufficient and sustained immune recovery and control of HIV with the use of anti-HIV therapy. The guidelines around maintenance therapy, and stopping maintenance therapy, are outlined in Project Inform's *OI Chart*.

Some people with recurrent herpes infections will take long-term anti-herpes therapies to prevent recurrences. Similarly, some people who have had trouble with recurrent fungal infections will take long-term anti-fungal drugs to prevent recurrences. In both of these cases, maintenance therapy is somewhat controversial. This is because the organisms can develop resistance to the drugs, leaving few viable options for

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treatment if or when a serious infection occurs. When herpes or fungal infections become recurrent, however, it may come down to a quality of life issue and long-term therapy may be the only viable option for a person. Weighing the risks and benefits of these approaches carefully is critical to making the right choice. Some will choose to risk losing viable treatment options to alleviate the problems of recurrent infections. Others will choose to simply treat the recurrent infections when they happen in hopes of preserving the benefits of therapy.

Discussion

Regardless of where someone is at in the spectrum of HIV disease, there are things that can be done to prevent and/or treat opportunistic infections. Prevention of OIs is relevant to people at all stages of HIV infection. Prevention includes:

- maintaining good immune health,
- using anti-HIV therapies as appropriate to preserve the immune system from destruction by HIV and allow for immune recovery,
- preventing infections by the organisms that can cause OIs when possible,
- using treatments to prevent OIs when indi-

cated, and

- using treatments to prevent recurrences of OIs when indicated.

A plan for treating OIs includes:

- Seeing a doctor regularly (generally quarterly, but it might be twice annually for people who have good measures of immune health or monthly for people dealing with complications from HIV or medications) who specializes in HIV disease, is informed about HIV and has treated other people living with HIV. (An experienced doctor is better able to recognize symptoms of OIs and will be more familiar with preventive OI medicine and how to treat OIs.)
- Telling your doctor about all symptoms you are experiencing so that they can diagnose problems early.
- Treating infections as they occur, aggressively, following through on a course of treatment to completion and using maintenance therapy as indicated. This might include the need for life-long maintenance therapy to prevent recurrence.

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STI's (continued)

It is critical for people to be monitored closely by their doctors when attempting a treatment interruption in this setting. Guidelines for preventing opportunistic infections are a must. Additionally, expert guidance in interpreting the results of drug resistance tests should be sought in constructing a third line regimen.

Treatment interruptions: a final word

While the results of the STI studies conducted so far have not been what anyone might have hoped, they are also not a reason to be discouraged. Based on what has been learned from the various studies, there may still emerge a new strategy that will successfully allow people to spend more time off treatment without problems. The prospect of time off treatment and the chance for a reduction in side effects have been tantalizing enough that a number of people living with HIV

are still eager to enroll in STI trials or to attempt them on their own. There simply isn't sufficient data to say that any trial conducted so far or currently ongoing will offer a benefit to those attempting an STI. We do, however, know now that it is safe for at least some people to take a break from treatment for awhile. We also more clearly understand the conditions wherein breaks from treatment can result in problems. As stated in the lead article of *PI Perspective #36*, there are reasons to remain hopeful and to examine every piece of new information as the possible thread that will lead us one day to a cure.

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