

AIDS

INFO SOURCE

Treatment Issues & Information

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TREATMENT UPDATES

Strategic Drug Interruptions Will Holidays from Drug Cocktails Become a Reality?

By Matthew Sirinek MD

Treatment of HIV-positive patients with highly active antiretroviral therapy (HAART, antiviral drug cocktails) has been shown to reduce HIV viral loads to below the level of detection in the blood of many patients. This has allowed for a significant degree of immune restoration that allows HIV + patients to have productive and healthy lives. It has become clear, however, that HAART is unlikely to ever completely eradicate the virus from all reservoirs in the body.

Given that eradication of the HIV virus from the body appears unrealistic, attention has now focused on how to deal with HIV infection in the long term. One approach that has received a great deal of attention lately is structured treatment interruptions (STI). This approach suggests that individuals can intermittently stop their HAART for a

given amount of time sometimes as part of a given research protocol. Patients then alternate between being on and off therapy in structured intervals. Sometimes during the course of treatment, a physician may decide that treatment interruption is warranted. Certain guidelines should be followed and agreed upon by the patient. Close monitoring is necessary to ensure that the risks are minimized.

From the surface there are several justifications for STI. Firstly, it provides patients with a reprieve from taking these demanding and sometimes toxic medications. Perhaps the risks of developing lipodystrophy and metabolic abnormalities may be minimized due to less drug exposure. Also, patients may be less likely to develop treatment fatigue or long-term side effects that can lead to non-compliance and



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Neuropathy: A Common Complication of HIV Disease

By Daniel S Berger MD



The prevalence of HIV infection and those on treatment have increased over recent years and neurologic problems are among the most common of HIV-related complications. Antiviral treatment has been linked with toxicity to peripheral nerves and stage of HIV disease is also associated with various forms of neuropathy. Additionally, various opportunistic pathogens, such as cytomegalovirus (CMV) can directly infect peripheral nerves.

Therefore an increasing number of patients is being affected by this neurologic complication and likely to increase; an understanding of the various forms of HIV-associated neuropathy and improving treatment options is crucial for HIV positive patients and their quality-of-life.

There are various forms of peripheral neuropathy. The presentation can be acute or chronic. HIV neuropathic disease includes distal symmetric poly-neuropathy, inflammatory demyelinating polyneuropathy, autonomic neuropathy, progressive polyradiculopathy, mononeuritis multiplex and diffuse infiltrative lymphocytosis syndrome.

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Strategic Drug Interruptions

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viral resistance. Treatment interruptions can also result in large cost savings due to the expensive antiviral drug therapy being interrupted. Finally, while off HAART, rebound of HIV viral load to detectable levels is almost always observed. This viral rebound is definitely concerning, but it is theorized that allowing the virus to rebound temporarily may actually help to boost the immune response to HIV in the same way a booster immunization would. When the HIV viral load is undetectable in the blood there may not be enough virus circulating for our immune systems to mount an effective response. Thus, stopping therapy allows the virus to rebound in the bloodstream and the immune system, exposed to HIV may develop a stronger HIV-specific response to the virus. This might allow better control of viral replication in the future. However, one needs to understand that there are risks with treatment interruptions coupled with the knowledge that antiviral therapy on its own has certainly been successful at boosting patients' immune systems by depressing the virus. Indeed it is antiviral treatment that has saved many lives.

The immune response to HIV is still not completely understood. Recent studies have indicated that HIV-specific immunity diminishes with time in patients on HAART. Thus it appears that while HAART diminishes the amount of virus in the blood thereby helping the immune system to recover, the viral load may remain too low for the immune system to recognize and respond to it while on HAART. The immune system appears to be inhibited from responding to HIV when the drugs inhibit the virus to undetectable levels in the blood, and may not participate as much in helping to control the virus in concert with the drugs.

While STIs sound intriguing and are worthy of further studies, there are many unanswered questions that need to be answered before considering this option. First, the time intervals for being on and off HAART have not been adequately determined. There are many studies trying to determine this currently. Secondly, any time a patient is taken off therapy there is a risk of developing resistance to the regimen as the viral load increases. Thirdly, not every patient is ideal for STIs.

Patients with low T cell counts may not be suitable for treatment interruption. Their counts may be too low to adequately develop a good HIV-specific immune response off therapy resulting in a drastic decline in T cell counts when taken off their medications. This decline may expose them to unneeded risks for developing opportunistic complications. A recently reported study documented furthering AIDS events in some individuals during a treatment interruption study.

While STIs remain a very intriguing and enticing way to treat many HIV patients in the future, it is important to recognize that more studies are needed to determine the safety and efficacy of this treatment option. Not all patients will be suitable for this treatment option and many questions need to be answered before we consider using STIs in every day practice.

The notion that STIs may be beneficial came from the work of Drs. Lori and Walker and involved the famous "Berlin patient." This patient was placed on HAART during primary infection with HIV. He had two treatment interruptions, the second of which was not accompanied by a viral rebound. He elected to stay off therapy after that and no virus was detected in his blood 18 months later. He was found to have strong HIV-specific CD4 and CD8 cell responses. It is not clear if either the early intervention with HAART or the subsequent drug interruptions were responsible for the patient's ability to control his virus below the level of detection. He may have been naturally destined to be a long-term non-progressor. Nonetheless, this patient's success has led to trials of STI in an attempt to boost the HIV-specific immune response in patients on HAART.

Early reports suggested that STIs could have deleterious effects on the immune system. One study involved some chronically infected patients on HAART who had achieved undetectable viral loads. All of these patients stopped HAART and their viral loads all rose to above the pre-treatment levels within 2 weeks. This rebound of virus was also associated with a decrease in T cell counts.

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Mission Statement

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A Sampling of Nutrition Issues at the XIII Conference on AIDS in Durban, South Africa

By Cade Fields-Gardner, MS, RD, LD, CD

Though this year's XIII International Conference on AIDS in Durban, South Africa did not include the same level of scientific enthusiasm as in this conference's past venues, it was an opportunity to renew thoughts and efforts toward treatments that improve clinical well-being and quality of life. Nutrition issues in HIV disease were separated into social issues surrounding food security (ability to access) and the changes in nutrition-related lab values and body composition.

Changes in mortality and co-morbidities between 1996 and 1999 were explored in San Francisco. Increases in medication costs appeared to be offset by a large reduction in hospitalizations and other late-stage disease treatment. Hyperlipidemia (increased blood cholesterol or triglycerides) and pancreatitis were among the top growing concerns. Even the definitions of wasting and changes in body composition are evolving. Wasting of lean tissue without the weight loss that defines an AIDS diagnosis continues to be reported despite control of viral load.

Nutrient supplements were explored by a few presenters who suggested that body weight can be improved with the addition of supplemental calories. Additionally, fat malabsorption is an ongoing problem in HIV disease that can lead to nutritional compromise. Medications aimed at improving nutritional status, including body composition, showed economic and clinical benefit. The improvement in nutritional status in 15 patients in a skilled nursing facility associated with the use of growth hormone led to a shorter length of stay (mean = 8.6 months) than untreated patients (13.5 months).

Diarrhea continues to cause problems for patients taking the protease inhibitor nelfinavir (Viracept). In one report, 5 such patients were placed on a lactose free diet and compared to 3 more patients on a regular diet. Stool weight was decreased by about half on the lactose-free diet leading the authors to suggest that lactose may exacerbate diarrhea related to nelfinavir. Quality of life continues to be the "soft" issue for treatment. The impact of body composition changes on each of four quality of life domains was apparent in a European study of physical changes in 211 patients. Changes in sexuality were reported by patients with noticeable alterations in the neck and abdomen areas. Self esteem affected individuals (Carl Vogel Center, Washington, DC); but after treatment with nutritional counseling, acupuncture, and massage there was observed improvement in quality-of-life.

Altered metabolic parameters were explored in a number of presentations and included mitochondrial toxicity, altered blood lipid levels, hormonal alterations, and body composition changes. The ability to exercise may be affected by mitochondrial toxicity but authors of one small study from Copenhagen were unable to conclude an association between the medications and reduced exercise capacity. HIV+ patients with loss of subcutaneous fat in this study had a higher level of blood lactate (a marker of mitochondrial toxicity) and lower exercise capacity. Hyperlipidemia (both high cholesterol and high triglycerides)

has caused increasing concern in patients on HAART, particularly with the use of protease inhibitors. Lipid-lowering agents have been explored as a means to control high blood fats and the potential consequences of cardiovascular disease, pancreatic function compromise, and avascular necrosis of bone tissues. One group reported on the effect of altering antiretroviral therapy in 265 patients. Both cholesterol and triglycerides were decreased after 3 and 6 months of switching antiretroviral therapy.

Changes in physical features was the subject of several presentations. There is much frustration with the lack of a clear definition and diagnoses of altered fat deposition syndromes. Presenters differed in their approach and audience members differed in their opinions about the characteristics and diagnostic techniques to differentiate altered fat patterns for normal weight gain or weight loss. Risk factors for the development of altered fat patterns were reported by several groups. One group looked at 92 patients who were diagnosed with altered fat patterns and suggested that the most apparent risk factors included duration on protease inhibitor therapy, age, and the duration of time that viral load was higher than 200/ml.

Three presentations evaluated the use of standard anthropometry (measurements of body circumferences and subcutaneous fatfolds) to identify patients with such body changes. Though waist circumference was the best predictor of visceral fat, the measure alone does not differentiate between normal obesity and an increased visceral fat compartment. It became apparent that it is important to standardize alternate sites for anthropometry to better identify and quantify altered fat patterns versus normal weight changes. Breast enlargement was explored in one small study of 5 patients (4 were men) who presented with this symptom. Though this study was a small one, the authors suggested that painful breast enlargement was not specifically related to protease inhibitor therapies nor to the presence of other physical alterations.

As we learn about controlling HIV disease, we now face some of the long-term survivor issues that are seen in other chronic and inflammatory diseases. Once again, HIV-related research is becoming a "space program" of exploration from which we expect to create a lot of "Corning Ware®" that will benefit clinicians and patients in many disease states. Watch for the next issue of AIDS InfoSource which will include information on hormonal alterations and treatments reported at the XIII International Conference in Durban.

To better serve our patients, the nutrition program at NorthStar Medical Center currently uses alternate anthropometric measures to estimate the volume of the visceral compartment, subcutaneous compartment, and total area at the same level as MRI and CT scans that are currently being used to determine visceral adiposity.

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President Bush's budget proposal includes deep cuts for many health care programs for people without health insurance. While President Bill Clinton championed these programs, the present administration plans on phasing out these programs. Many state-based programs that provide drugs to uninsured people with HIV disease have placed new restrictions on benefits and enrollment due to being short on funding. Much of AIDS-related funding is through discretionary means whereby Congress must okay yearly. To alert Bush on your comments regarding HIV/AIDS service and research funding one may call the White House hot line at 202-456-1111, press 0 and leave your message.

Another lipodystrophy study conducted in Spain was published recently in the British medical journal, *Lancet*. All 494 patients were antiviral naïve at start of study and were started on protease inhibitor based cocktail. 17% of patients developed lipodystrophy at 18 months. Increased risks for lipodystrophy included female sex, increased age and duration of antiviral therapy. And while the cause appears to be multi-factorial problem, it was also observed that d4T (Zerit) was associated with significant risks for lipodystrophy (loss of fat) and indinavir (Crixivan) with increased central obesity (protease paunch). These findings are similar to other cohort studies.

The race for the development of a second generation NNRTI (non-nuke) continues, however, not without drama. While Dupont pharmaceuticals has DPC-083 in phase II studies, and phase III to begin by early summer, the company is up for sale, which leaves us with uncertainty regarding continued development of the drug. One hopes that

the next purchasing company will have the experience and funding to keep up with Dupont's track record, as it succeeded in developing Sustiva quickly and efficiently. On another front, the Agouron Pharmaceutical division of Pfizer has met with some stumbling blocks in trials with Caprivirine, their novel second generation non-nuke. Animal studies demonstrated some toxicity and inflammation to blood vessels (vasculitis). The sponsor is committed to developing this agent and is working with the FDA to complete its' prior studies as well as further pharmacokinetic (blood drug levels) investigations. The next phase of clinical trials are hoped to begin early next year (2002).

Pegylated interferon combined with ribavirin for treatment of hepatitis C is more effective than standard interferon. The new Schering-Plough form of interferon was approved by the FDA in January with Hoffman La-Roche also on the way. The PEG interferon named because of its attached molecule of polyethylene glycol improves its' half life enabling patients to dose the drug only once per week. The way in which the pegylated version's approval occurred makes little sense as one can only obtain ribavirin with the older interferon version; ribavirin in combination with the PEG form is clearly superior. Other drug treatments for hepatitis C are also on their way. They include interleukin 10 as well as other inhibitors against hepatitis C such as protease inhibitors.

Drug resistant stains of HIV are increasing among the newly infected. In a study reported at the 8th Conference on Retroviruses and Opportunistic Infections held in Chicago this year, 14 percent of patients newly infected with HIV were found to have resistance to drugs of one particular class, increased from previously reported 3.5%. The trends showed that East Coast had increased resistance compared to the West Coast; the study was conducted in Dallas, Denver, San Diego, New York, Los Angeles, Birmingham, Seattle, Montreal and Vancouver. Two conclusion remains

clear: drug resistant patients are spreading virus through unsafe sex and HIV-infected individuals need to continue practicing safe sex – “barebacking” is dangerous and persons promoting this form of unsafe sex are irresponsible.

More HIV+ individuals are looking at plastic surgery to help combat the disfiguring consequences of lipodystrophy, reported at the World Congress on Liposuction Surgery. Cosmetic surgeons are busy removing buffalo humps and other fat deposits. Cosmetic surgeons should work in cooperation with the HIV specialist or HIV antiretroviral prescribing physician.

Morbidity and mortality rates of aggressive squamous cell skin cancers appear to high in HIV positive patients. In a study reported at the American Society for Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology. Of the 10 patients who were doing well with HIV infection developed these aggressive skin tumors; 7 developed metastases and 5 died at an average of 11 months. The study suggests that HIV-positive individuals who develop aggressive squamous cell skin cancers should be treated with surgery followed by radiation therapy.

The triple nuke regimen of AZT (retrovir) + 3TC (epivir) + Ziagen (abacavir) was found to be as effective in treatment of antiviral naïve HIV+ subjects as compared to the protease inhibitor based cocktail of indinavir (Crixivan) +AZT/3TC - recently published in the *Journal of the American Medical Association* (March 7, 2001). In this study 562 patients who had never experienced HIV antiviral treatment were randomly assigned in a double blind to the two cocktail regimens. Hypersensitivity reactions were reported in 7% of patients taking abacavir consistent with other studies. Interestingly, 2% of patients not taking abacavir, but on indinavir were reported by their investigator to have possible abacavir reactions based on the presence of rash alone.

Neuropathy

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Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathy (DSP) is the most commonly observed form of peripheral nerve complication of HIV disease. It affects greater than one third of HIV-positive persons. It occurs in individuals irregardless of specific T cell number or viral load but in general seems to be more common among patients with later stage disease. Its' manifestations include both paresthasias (abnormal sensations such as numbness and tingling) or aching of hands and feet in the stocking-glove distribution and hyperesthesia such as increased sensitivity to walking barefoot or contact with bed sheets. Other associated symptoms include numbness, tingling, burning and intermittent sharp pain in the feet but can also affect fingers of the upper extremitities.

On neurologic exam of patients with HIV-related DSP there is often absent or depressed ankle reflexes relative to the knees. Other common signs include hyperactivity of the knee relexes, normal position (proprioception) , increased vibratory perception and decreased pinprick and temperature of the stocking glove areas.

Various mechanisms have been proposed to explain the cause of DSP. Direct infiltration of HIV in myelinated nerve fibers of peripheral nerves have been observed, but not considered likely to be the primary cause. Other possibilities include vitamin B12 deficiency, cytokines such as interleukin 1 and tumor necrosis factor, wasting and malnutrition, and various drugs and neurotoxins.

Antiretroviral agents have been well documented to demonstrate dose dependant toxicities to peripheral nerves. Stavudine (d4T), zalcitabine (ddC) and didanosine (ddI), all of the nucleoside reverse transcriptase inhibitor class, are the major drug sources. Additionally, the incidence increases with further immune system disease. Often the neuropathic symptoms are reduced with dose reduction or withdrawal of the offending medication. However clinical

improvement may take several months after these treatment adjustments..

The nutritional deficiencies and vitamin components as being a possible component for neuropathy risk are yet an additional reason for keeping up with individual's nutritional status and ensuring that certain vitamins are at optimal levels for patients on antiviral medications. It is not uncommon for this author to administer vitamin B12 infections periodically to HIV- positive patients. Other vitamin supplements that have demonstrated benefit to improving neuropathy symptoms include other B vitamins, folic acid and L-carnitine.

Treatment of DSP is based on symptoms Correcting nutritional deficiencies and correcting metabolic abnormalities are often useful. Non-steroidal anti-inflammatory agents, tricyclic anti-depressants such as amitriptyline, used singly or in combination are often useful. Amitriptyline is usually started at low dose of 10 mg nightly and increased gradually, however anticholinergic side effects and sedation are not uncommon side effects. Anticonvulsants such as phenytoin(Dilantin), carbamazepin (Tegretol) and gapapentin (Neurontin) may also provide relief from symptoms. Recently lamotrigine, a newer anticonvulsant has shown significant pain reduction in HIV associated neuropathy. However skin rash is not uncommon and severe anaphalactoid like reactions have been reported.

In a placebo controlled trial alternative therapy with Peptide T has been shown to be ineffective in relieving pain in DSP. Recombinant human nerve growth factor (rNGF), effective in treatment for diabetes associated neuropathy has shown mixed results in clinical trials of HIV infected patients with DSP .Preliminary studies using acupuncture as adjunctive treatment for neuropathy has shown some promise.

The 8th Conference on Retroviruses and Opportunistic Infections held in Chicago in February 2001 had many of its' plenary lectures related to new targets for HIV therapy. The process of blocking viral entry to the human host cells were focused upon, some agents are currently in clinical trials Much of the research in the basic sciences and molecular-level virus and host cell interactions hold fascinating interest and great promise.

A recent report on HIV positive women and depression was published in the March 21st issue of JAMA (Journal of the American Medical Association). Of 765 HIV- positive women, 42% had chronic depressive symptoms and 35% with intermittent symptoms.

Patients were followed for 7 years.

During this time period, women with chronic depressive symptoms were 2 times more likely to die than those with less or intermittent symptoms. Also women with depression had greater decreases in their T cell counts. Like other studies with women and HIV many in this study also were not treated with standard of care HAART cocktails. Perhaps being well treated for HIV would probably improve prognosis and decrease depressive symptoms.

The Journal of AIDS reported recently that more time spent with patients and their physician discussing HIV-related issues resulted in better communication about the specific issues. The study also demonstrated an association of longer duration of the physician-patient relationship and having a female physician. Also shown was that gay or bisexual physicians were associated with better communication about HIV-specific issues no matter what the sexual orientation of the patient.



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Pipeline Mania

An Update on New and Promising Anti-HIV Drugs

By Daniel S. Berger MD

Kaletra

The new protease inhibitor, Kaletra (Lopinavir/ritonavir or ABT-378/ritonavir) has recently become available on the market for a relatively short period of time. Because of its' easy tolerability and low pill burden, it is being used widely by many clinicians. It has been studied in naïve and protease-experienced patients in combination with non-nucleosides. The data holds up regarding the advantages of using this protease inhibitor in certain situations. Being new, Kaletra has not been studied as extensively as other agents, and its' appropriate use as first line treatment, and questions regarding the proper sequencing of this drug because of cross-resistance to other protease inhibitors have been raised. However, it is well tolerated and has become a useful addition to the antiviral armamentarium. Like most new drugs coming to market, the previous studies are designed to get the drug FDA approved and available. Later studies and further clinical experience will add to our understanding.

Tenofovir DF

Gilead Sciences, the developer of this new anti-viral agent is on track for submitting its' NDA (new drug application) by the end of June. This means that the drug should be approved and on the market by late fall, assuming things go smoothly with the FDA. This drugs has many advantages and we anticipate that it will be prescribed widely. Tenofovir DF is part of a new class of drugs called nucleotide reverse transcriptase inhibitors. Its' active metabolite has a half life between 10- 30 hrs (duration of drug lasting in the blood stream) and the intracellular half life is greater than or equal to 30 hours, therefore can be given at convenient once daily dosing. In vitro (test tube) toxicity studies show tenofovir having little effects on the mitochondrial enzymes and not limiting the mitochondrial DNA,

predictors of mitochondrial toxicity. (Most current schools of thought believe that it is this toxicity to mitochondria that causes lipodystrophy complications in HIV disease) thus earning it as an attractive choice for use in antiviral cocktails, once available.

Also, tenofovir has activity against HIV with various AZT, ddI, and ddC-associated mutations and shows increased activity against HIV with 3TC resistance.

HIV infection who have failed prior antiretroviral therapy regardless of their CD4 T cell count or viral load. The program previously did limit patients to having low CD4 counts.

DPC-083

A second-generation non-nuke, DPC-083 is continuing in clinical trials. The first phase II studies are being conducted in Europe and at only 5 sites around the US, one being at NorthStar Medical in Chicago. This particular protocol is studying individuals who are failing their first regimen containing a non-nucleoside and is still open for enrollment. As a non-nucleoside, DPC-083 has similar potency to Sustiva (efavirenz) against wild type virus, however it has other significant advantages: the drug is effective for virus that is potentially resistant to Sustiva or Viramune (nevirapine) including against the infamous K103 mutant, and 2-11 times more potent than Sustiva against other potential resistant virus. It has a long half-life (duration of drug in the blood stream), administered once daily. Thus far the drug has been found to be well tolerated and side effects have been found to be of minor severity and of short duration. Dupont Pharmaceuticals is currently up for sale. We hope that a pharmaceutical company experienced in HIV drug development acquires Dupont and will show the same commitment, ability to develop further antiviral options and continue in its support of the HIV community.

T-20

T-20 is another novel agent in a new drug class called fusion inhibitors. T-20 blocks the ability of HIV to combine or fuse with the CD4 receptor (T-cell). Preliminary studies have shown that T-20 was effective in patients with resistance to other antiviral agents. Cross-resistance is unlikely due to the unique mechanism of action. Because the chemical structure of this agent is a chain of amino acids, it is



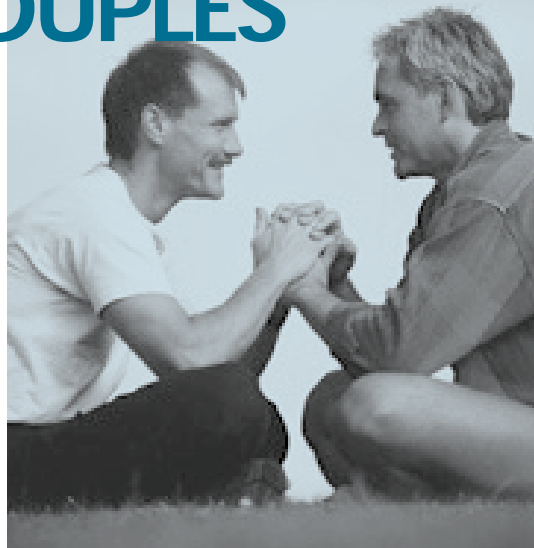
Indeed an earlier study (Study 902) demonstrated antiviral effect of this agent; 94% of the study patients had NTRI resistance mutations prior to study. The most recently reported study (protocol # 907) enrolled more than 550 treatment experienced patients; there was significant viral load reduction observed in this group who had tenofovir added to their existing drug cocktail and 45% achieved viral loads below 400 copies/ml. Tenofovir is currently available on a compassionate program which was recently broadened on April 24, 2001. The program now allows patients with

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RELATIONSHIPS WITH HIV-IMPACTED COUPLES

Resolving Conflicts Friendly Advise

By Greg Sarlo Psy-D
Licensed Clinical Psychologist



Negotiating conflicts during the course of a relationship can be difficult; facing the added stress of HIV is usually more imposing. Often times many issues are not discussed because HIV is present. In many instances the HIV becomes the focus between couples and basic communication skills are lost in the shuffle. We often think that because HIV is such a big issue and we are handling it, other issues such as basic communication and conflict resolution may not seem as important. But, in reality, the opposite is true.

When we first look to enter a relationship, we do so with the reasonable hope that it meet our desires for companionship, emotionally and sexually. We expect mutual growth. In the beginning, we go out of our way to accommodate each other. Pleasing our partner is paramount and our love often outweighs petty annoyances.

After a short period of time in a relationship, being on our best behavior becomes a strain, and conflicts surface. For instance, the HIV positive individual may hold back in discussing test results he has just received for fear that it could burden or worry their newly gained partner. Unfortunately, this lack of communication bottles up and the couple may eventually have a major disagreement. The first major disagreement can lead to a premature breakup, or be so unsettling that we develop unspoken agreements not to touch certain topics. But avoidance of conflict, or certain topics, restricts the areas in which we interact, and decreases feelings of closeness. Our attempt to avoid confrontation of this issue actually increases the risk for future problems brewing and boiling. But not talking

about how we feel, leads to increasing distance in the relationship, especially the couple impacted by HIV. So much of the relationship can become prematurely focused on HIV. However, HIV in some situations should be focused upon. This fails to occur due to denial. In either case, avoidance of conflict or rejection is often the primary cause. So how can we approach conflicts with more confidence that we will be able to resolve them? By facing the conflict!

Conflict in any relationship is inevitable. Much of how we resolve our conflicts is determined by how our families did so when we were being raised. It is how we deal with the conflict that determines whether or not our relationship is damaged or strengthened. If we anticipate the conflict, we won't feel so overwhelmed when we encounter differences.

Conflict is healthy. Differences exist. When we resolve them successfully, we feel closer. Although it may feel threatening to acknowledge differences, intimacy flourishes. It is by revealing who we really are, rather than projecting an image of how we would like to be seen, that we continue to grow in our relationships.

Changes are inevitable as one grows older, and a relationship develops. There are career opportunities and financial obligations outside of the relationship; outside interests and friendship networks shift, your health, HIV, and different HIV status may become an issue, and levels of sexual involvement change. In

other words, expectations from the relationship is altered on many levels. This is particularly true if the health status of the HIV

positive person changes. One may wonder whether or not one will be able to adjust successfully.

Maintaining a sense of yourself as an individual while still affirming the importance of your relationship is a significant task for any member of the couple regardless if you are HIV+, or not. Men are socialized to function independently, so a male couple may have a difficult time finding the balance of "who am I," "who are you," and "who are we together?" A sense of self allows a genuine exchange between you and your partner. You cannot really feel close unless you experience yourself as a separate individual. Otherwise, there is no "you" to appreciate the closeness. Similarly, taking your relationship into consideration, not just your own personal desires, allows you to weather the differences that inevitably arise.



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STUDIES

- *Most studies provide for antiviral drugs, labs and Dr./study visits and are free of charge to the patient during the study.*
- *Think about being part of a study, or referring a friend, that is not on effective treatment*
- *Gain access to the newest generation of up and coming treatments.*

Trizivir + Efavirenz (Sustiva): Protocol ESS40013

This is a 96 week phase IV study of treatment with Trizivir + Efavirenz. Initial treatment for 48 weeks is then followed by an additional 48 week randomization to open label maintenance treatment with Trizivir with or without Efavirenz. This study is for naïve patients, or individuals never having been treated with antiretroviral medications.

Second Generation Non-nucleoside Phase 2 Protocol 083

This is the new second generation non-nucleoside reverse transcriptase inhibitor (DPC-083) - study that is randomized double-blind of two doses of DPC 083 in combination with open-label nucleoside analog reverse transcriptase inhibitors in HIV-1 infected patients who are failing treatment with a non-nucleoside reverse transcriptase inhibitor-containing regimen. This new agent is considered a true second generation NNRTI, promising to be an effective antiviral against resistance mutants of other currently available non-nukes

FTC (Emtricitabine) vs d4T

FTC is a new potent nucleoside analog. In-vitro studies demonstrated FTC to be more potent than 3TC. This study is a randomized double blind study comparing two arms: FTC +ddI and Sustiva vs d4T + ddI + Sustiva. Patients must be antiretroviral naïve and have viral loads greater than 5000 copies/ ml.

Tenofovir DF (PMPA Prodrug) Protocol 903

Tenofovir is part of a new class of agents called nucleotide reverse transcriptase inhibitors. This study is for naïve patients, or patients that have never been on HIV therapy. It is a randomized double-blind in combination with 3TC and Sustiva vs. D4T, 3TC and Sustiva. The study is a 48 week study, but promises to continue till the drug's approval.

PMPA Prodrug - Tenofovir Protocol 907 (Phase 3)

This is a part of the new class of agents called nucleotide reverse transcriptase inhibitors. The study keeps patients on their already stable cocktail but adds this

new potent agent to the regimen. This phase III, 48 week study is for patients who have been on stable therapy and who have viral loads between 400 and 10,000.

Tenofovir 910

This is simply the extension phase of several Tenofovir studies. Patients who are or were on phase II or phase III Tenofovir studies are transitioned into this protocol. They continue receiving open-label drug, while long-term safety and monitoring continues.

Lipodystrophy and/or Elevated Lactate Levels Switch Study Protocol ESS4000

This study is to assess the regression of hyperlactatemia (elevated lactic acid levels in the blood) and to evaluate the regression of lipodystrophy in HIV-1 positive individuals (TARHEEL Protocol). Experienced patients will be switched, open label to zigen from d4T. Naïve patients will be placed on Combivir. Intensification will be permitted in the event of loss of virologic control.

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The following list of studies are available at the NorthStar Medical Center Dan Berger, MD and Associates

For further information or participation please call 773\296-2400

Pipeline Mania

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easily broken down by stomach acids. Thus the drug needs to be administered by subcutaneous injection. The drug, developed by the small biotech company, Trimeris sold marketing rights to Hoffman La Roche. This larger pharmaceutical company will definitely aid in its faster development and production. T-20 will also become available on a limited compassionate track program.

TMC-120

This agent is part of a new non nucleoside agent that is being developed to target both wild type virus as well as resistant strains. The developer is a Belgian company called Tibotec. Other compounds in its' development such as a protease inhibitor (TMC-126) also targets resistant virus. Reported in last years 40th Interscience Conference on Antimicrobial Agents, has potent activity against non nucleosides resistance

including nevirapine (Viramune), efavirenz (Sustiva) and delavirdine (Rescriptor). Early results of a phase 1-2 trial using two different doses of TMC-120 demonstrated a 1.4 log decrease in HIV RNA and an increase in 120 CD4+ T cells in both treatment groups after a short 7 day study period.

DAPD and DXG

These agents are being developed by Triangle Pharmaceuticals. DAPD is a nucleoside reverse transcriptase inhibitor that is metabolized to its' active compound DXG. DXG reaches higher blood levels than those of DAPD. A phase 1-2 study of patients who have previously failed treatment with either AZT/3TC or d4T/3TC containing regimens were studied for 14 days of treatment with DAPD. The trial demonstrated viral load decreases of 0.5 logs for 200 mg and 300 mg twice daily and 1.1 log decrease for the 500 mg dose.



L2-7001 - Interleukin-2

This is a phase II, 6 month study examines 3 doses of a new formulation of IL-2, that appears to be three times more potent and with less side effects than the currently used IL-2. The study eligibility includes patients with T cell counts between 300 and 500 cells. Viral loads should be less than 10,000 copies. Patients will be randomized to receive either the L2 form of IL2 or Proleukin IL2 twice daily (split dosing) for 5 days every two months. Some patients will be asked to be tested for IL2 blood levels.

Lipodystrophy and Fat Redistribution Syndrome

This research involves testing to examine the various relationships of a variety of factors that may contribute to the development of lipodystrophy and fat redistribution. The initial stage of the study is retrospective and examines the patient's past medical history. The second phase of the study will include DEXA testing for body composition as well as single slice abdominal cat scanning to examine visceral (internal) body fat development.

Anogenital Herpes Treatment with Resiquimod (R-848)

This is a phase II randomized double-blind dose frequency response study of topical resiquimod gel applied to the herpes lesions once, twice or three times per week for recurrences to prevent

future recurrences. Resiquimod is a topical treatment that works by stimulating one's own immune system to act against the herpes infection. This is for patients who are not immune compromised (HIV-negative).

DMP 266 - Sustiva + Crixivan

DMP 266 is a potent non-nucleoside reverse transcriptase inhibitor (NNTRI) that inhibits HIV production in HIV infected cells. A 2 year phase II/III multicenter, randomized, open-label study to compare antiretroviral activity and tolerability of three different combination regimens (DMP 266 + Crixivan, DMP 266 + AZT = 3TC, Crixivan = AZT + 3TC) in HIV-infected patients. Patients must be asymptomatic or mildly symptomatic, have a CD4 cell count greater than or equal to 50 cells/mm, and a viral load greater than or equal to 10,000 copies/mL. Patients will have received no prior treatment with DMP 266, 3TC, nevirapine, delavirdine, or any protease inhibitor.

Passive Immunotherapy with CMV Intravenous Immunoglobulin

CMV IVIG is a preparation that contains high titers of antibodies of CMV (Cytomegalovirus). CMV is often a cause of opportunistic disease in AIDS.

This off-label treatment is available to patients with CMV disease (i.e., CMV Retinitis, esophagitis, gastritis, or systemic disease, etc).

Passive Immunotherapy with Intravenous Immunoglobulin

IVIG is a lyophilized preparation of intact immunoglobulin G (IgG) from pooled plasma and is not chemically altered. This broad range of antibodies is capable of neutralizing microbes and toxins against bacterial and viral antigens of various infectious diseases. This off-label treatment is available to patients with recurrent bacterial infections and/or history of an opportunistic disease. IVIG is administered monthly with close monitoring.

Interleukin-2 (IL-2)

Open-label interleukin-2 is a cytokine (natural substance produced by cells) that may stimulate T-cells increases. This off-label use of this drug for patients with CD4 T-cells greater than 100. The drug is administered by subcutaneous injection daily for 5 consecutive days every 8 weeks.



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Neuropathy

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Inflammatory Demyelinating Polyneuropathy

Inflammatory demyelinating polyneuropathy (IDP) may occur as either rapidly progressive (acute) or slowly progressive (chronic) forms. While this is generally an infrequent form of neuropathy, it tends to occur in asymptomatic HIV infected individuals but also observed during primary HIV infection (acute seroconversion). The clinical hallmarks are severe muscle

weakness of two or more extremities but may also include diaphragmatic muscle involvement in severe cases. Additional facial weakness, bilateral is also occasionally seen.

A lumbar puncture (spinal tap) for cerebrospinal fluid (CSF) analysis demonstrates a pleocytosis (abnormal white

blood cells) of 10-50 cells/mm³ and protein elevations of 50-250 mg/dl. In immune devastated individuals, PCR analysis for CMV DNA may be present. Electrophysiologic testing is often positive for demyelination.

The etiology of IDP includes autoimmune mechanism but in the severely immune compromised, CMV neurologic infection is often the cause. IDP is primarily treated with immunomodulation including corticosteroids, high dose intravenous immune globulin (IVIg) or plasmapheresis. In late stage AIDS, prompt treatment with aggressive anti-CMV therapy should be initiated i.e. ganciclovir (Cytovene), foscarnet or cidofovir (Vistide), alone or in combination.

Autonomic Neuropathy

Autonomic neuropathy is occasionally observed in HIV-infected individuals. The autonomic nervous system regulates many body functions and is divided into two components: Parasympathetic and Sympathetic. With parasympathetic involvement, resting tachycardia (increased heart rate), urinary dysfunction and impotence can be observed. Sympathetic autonomic dysfunction is characterized by diarrhea, orthostasis, (light headedness when standing) syncope (fainting spells) and anhidrosis (decreased sweating) are noted. Various drugs have been associated with autonomic dysfunction and include pentamidine, vincristine and tricyclic antidepressants. Treatment is through management of signs and symptoms.

Mononeuritis Multiplex

Mononeuritis multiplex (MM) occurs in both, individuals with low CD4 and is usually more severe, as well as in patients with CD4 counts above 200 count. It is characterized by asymmetric and proximal involvement (upper part of arms or legs) of peripheral nerves with tendon reflexes remaining intact. Sensory and or motor deficits are both observed in MM and may include cranial or peripheral nerves. In patients with healthier immune status (CD4 counts > 200 cells/mm³), symptoms resolve spontaneously or with immunomodulatory therapy within several months.

When occurring in severely immune compromised patients, nerve involvement is more extensive with rapid progression, not dissimilar to severe IDP or progressive polyradiculopathy. Empiric therapy for CMV has been shown to be effective in treating affected patients with MM.

Progressive Polyradiculopathy

Progressive polyradiculopathy (PP) occurs in late stage AIDS, affected individuals often have a history of prior opportunistic infections especially CMV end organ disease. It has a rapidly progressive course if treatment is not administered, thus prompt diagnosis is key. PP is characterized with pain and paresthesias (abnormal sensation) in the cauda equina (lower spine) distribution followed by flaccid paraparesis (weakness), loss of reflexes of the lower extremities, mild sensory deficits and sphincter dysfunction. Urinary retention is seen in the majority of patients. If treatment is not initiated mortality rates approach 100% within 4 weeks after the onset of symptoms.

Laboratory testing demonstrate electrophysiologic abnormalities consistent with lower extremity and lumbar paraspinal muscle denervation. Cerebrospinal fluid analysis often reveals elevated white blood cells from 17 to more than 2000 cells/mm³, elevated protein and low glucose levels below 40 mg/dl. Analysis of CSF for CMV DNA by PCR is often positive, but aggressive anti-CMV therapy should not be halted the test for CMV is negative since almost all autopsied patients with PP demonstrated CMV infection despite negative serology (testing).

The etiology of PP points to direct infection by CMV. CMV has been isolated in CSF, affected nerve routes and autopsied endothelial, Schwann and ependymal cells in patients with PP. Additionally, response to prompt anti-CMV therapy also lends credence to a CMV based etiology of PP.

Treatment of PP should employ both ganciclovir and foscarnet in combination.

Both agents are capable of passing through the blood brain barrier. If treatment is initiated early and prior to nerve root necrosis occurs, clinical improvement or stabilization can be observed in 50% of affected patients.

Conclusion

Since the symptoms of peripheral neuropathy can be debilitating, effective treatment with appropriate therapy can often improve the quality-of-life of affected patients. Research of effective treatment for peripheral neuropathy with conventional and alternative therapies have not always shown optimal results. Some of the treatments involve a trial & error, with stopping or titration of medication till benefit is reached in each specific patient. Alternative therapies with acupuncture and massage are sometimes beneficial, does not involve further pill taking and is often worthwhile for some patients. Further research is crucial to improve our understanding of neuropathy so that more effective treatments become available for this incapacitating disorder.

Preliminary studies using acupuncture as adjunctive treatment for neuropathy has shown some promise.

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Conflict is inevitable but one can be skeptical whether or not it is all that healthy. We need a way to talk about problems, instead of arguing about them and then withdrawing. One way to improve the relationship is for both partners to improve their ability as a couple to empathize, express, and avoid pitfalls that commonly escalate conflict. One way to achieve this is through "couples therapy".

Many people think that a couple should only enter therapy when there is something seriously wrong in the relationship or when there has been a health crisis. Typically, when it reaches this stage, it may be too late: dysfunctional avoidant patterns in the relationship might be beyond the point of no return. There are times when, of course, you are too upset to remember any of these skills, and you end up in arguments and withdraw for while anyway. But instead of ignoring the conflict and letting it build up again, you need to learn how to approach each other to work through your differences.

The following are some ways to resolve conflicts in a relationship:

1. Try not to be so defensive

When your partner is angry with you, it may be difficult to keep still while he expresses his feelings. But when you are preoccupied with defending yourself, you stop listening. You may try to convince him there is no reason to be upset by giving excuses, arguing about the facts, offering advice, reassurance, counter-complaints, or analyzing his behavior. Remember, a defensive response is basically an attempt to get your partner to stop feeling, so you won't feel blamed.

2. Try to listen more

Listening seems quite simple and passive, yet it can be a powerfully active process. It takes a lot of concentration to listen accurately, especially when your partner is upset with you. Remember you must pay attention. The closer attention you pay to him, the quieter you become yourself. Since he is able to explain how he feels without being interrupted, your partner will have a

better sense that he feels he's getting through to you. Eventually he will be more apt to pay you attention, himself.

3. Remember to paraphrase

Paraphrasing consists of telling your partner, in your own words, that you have heard him. For the moment you don't have to justify or answer yourself; just say what you understood. Once he feels heard, it will be easier for him to listen to you.

4. Try to reflect the feelings of the other person.

You should always try to imagine what your partner is feeling. That does not mean you need to make assumptions or psychoanalyze or tell him what he is really feeling. It simply is a way to find out if you understand what he is feeling.

5. Empathize

Empathy is the ability to put yourself in your partner's place and imagine how you would feel if you had the same experience. Some ways to do this are to observe his body posture, listen to his voice, look at his eyes, and say what you imagine he is feeling. It is not necessary that you are right. Your concern and effort is to understand him and help him figure out how he feels.

6. Listen for positive intent.

Positive intent is the wish for better relations, which lay behind many hostile interactions. Hurtful statements often arise from a desire to demonstrate one's own pain. Remember that behind the expression of pain, there is a wish that things could be different. You can use your own feelings as a clue to what your partner may feel. If you feel hurt, he probably does too.

If you are too upset to listen, you, more than likely, will go through the following cycle: you have a quarrel, in which neither of you feels heard, you withdraw for a while, and then you try to make up in some fashion.

During the quarrel it is very difficult to listen. Both of you feel frustrated because neither feels heard. You may exaggerate your points, dredge up past

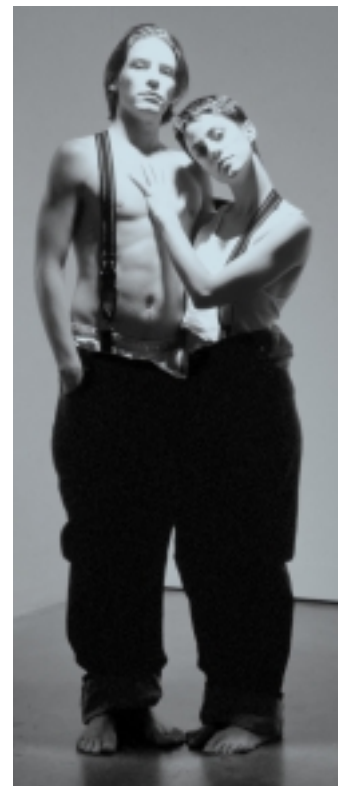
conflicts, and say spiteful things to demonstrate your hurt. One doesn't have to end the world or the relationship due to a little tiff. What typically happens next is that you both withdraw for a while to cool off. Sometimes you both need a "time out" from one another. That is ok. One reason for withdrawing after a fight is the fear that talking about what happened will just start the quarrel all over again. Withdrawal is one strategy for keeping out of each other's way for a while.

Making up is very important. Simply ignoring the conflict leads to increasing distance, and it is likely that the same issue will build up again. Though you both may have said a lot of foolish things, the quarrel may have revealed some hidden resentments that need to be discussed. So you need a way to get back together and talk about what happened.

One way is to approach your partner to see whether or not he is ready to talk about your argument. Disclosing the hurt and fear behind your anger will help you listen to each other. Acknowledging your own role in escalating the conflict can also help. Ask yourself the following questions after a conflict:

- 1. Did you give advice?**
- 2. Did you make excuses?**
- 3. Did you accuse him?**

If you practice these techniques with one another, you should see a difference in your communication with one another. Of course, there can be other longstanding issues that may need the help of your favorite Psychologist; if the problems persist, consider giving him or her a call.



SCIENCE BEGETS POLITICS

THE FUTURE OF EMBRYONIC STEM CELL RESEARCH

By Daniel S. Berger, M.D.

It is unfortunate that ongoing research, previously approved by Bill Clinton, is being suspended. Potentially promising new therapy may be blocked by the current presidential administration from being investigated. A new avenue of research, using embryonic stem cells, has shown encouraging results for future therapeutic applications for many diseases including, Alzheimer's, Parkinson's disease, diabetes and leukemia, to name a few. In particular, fetal bone marrow cell transplantation holds promise for the treatment of AIDS and other forms of immune deficiency

Embryonic stem cells are building blocks that normally give rise to immune system fighting cells.

They originate in the bone marrow, divide into daughter cells and eventually differentiate into many different types of components making up much of our immune system. Immature stem cells taken from embryos or fetal tissue can be infused intravenously into individuals that have immune systems problems, (such as HIV-infected or individuals with AIDS). The purpose of such research for example is to investigate the potential replacement or repair of immune deficiencies.

While we have recently been faced with this new presidential administration, new policies follow. Many of these changes are disturbing to AIDS advocates, such as John Ashcroft's appointment as Attorney General. He has developed a track record of opposing many HIV-related issues. He is against HIV-drug programs and against equal rights for gays and lesbians. However, the appointment of Wisconsin Governor Thompson as Secretary of Health and Human Services has been a glimmer of hope for HIV supporters. Mr. Thompson's record on HIV issues for Medicaid eligibility and the AIDS Drug Assistance Program in his state was impressive.

However and not unpredictably, politics seems to be playing a central role in deciding the fate of embryo stem cell research, despite the potential for being safe and effective. The NIH (National Institute of Health) has been investigating this avenue of work and recently planned to have a meeting on April 25, to discuss the application of further federal funding. However the

meeting was cancelled since no decision has been made regarding the future of this research. The meetings' cancellation is worrisome and certainly motivates and provides steam to the opponents of this form of science.

The meetings' cancellation was to allow an outside committee to examine the implications of researchers applying for federal funds for stem cell research. Eventually the outside committee's approval will act as a prerequisite for applying for future funding. President Bush has also stated during his campaign that he is against stem cell research, but has yet to take any action.

One of President Clinton's first tasks after he took office in 1992 was to lift the moratorium on fetal tissue research.

Also, Clinton found a loophole for getting past the ban on destruction of fetal tissue. His legal interpretation provided the NIH the right for funding experiments as long as the NIH didn't actually destroy any embryos to acquire the tissue. Also if the tissue was acquired through private funding, then the cells could be used for research even if the scientists had destroyed the embryos to harvest the tissue. Previously, federal funding for this form of research has been restricted, related to anti-choice politics till Clinton lifted the ban.

However, George W. Bush is strongly against abortions and is anti-choice; we are therefore at risk again for a change in policy. Active demonstration to voice our opposition to any changes is necessary; this crucial form of research may hold many consequences for the lives and health of many individuals. A law restricting fetal research would set us back from this potentially beneficial and novel form of therapy.

There are channels to publicize one's opinion regarding AIDS funding and/or opinions regarding stem cell research. One can write their US senator or the White House. The White House also has a comment line at 202-456-1111, press 0 and leave your message or opinion.

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