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by Jeffrey T. Schouten, MD

42nd Annual ICAAC meeting

San Diego, CA September 2002

The 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) convened in San Diego with almost 10,000 infectious disease specialists from around the world in attendance. A major focus of this conference was bioterrorism and biodefense. This meeting covers all types of infectious diseases, so HIV is only a small part of the agenda. This report will focus on the HIV-related major developments reported at the meeting with a comment on biodefense and vaccine development for sexually transmitted diseases (STD). Dr. David Ho, also presented his findings, which were widely publicized a week before ICAAC, about the discovery of proteins that can inhibit HIV replication.

New Anti-HIV Proteins Identified

Dr. David Ho, published a report in *Science Express*, the online version of *Science Magazine* on September 26, 2002, that received extensive media coverage. For many years it has been known that a type of white blood cell, the CD8 lymphocyte, produces a factor that can inhibit HIV replication. This factor has been called the CD8 antiviral factor, or CAF. Dr. Jay Levy, has done a lot of research on this subject. Normally, CD8 cells kill infected cells by coming into direct contact with them. However, they also produce a factor, which is made up of small proteins, that can inhibit HIV replication in nearby cells. Many people have been trying to isolate this factor and now it seems that researchers in Dr. Ho's lab have identified these proteins. Using very elegant protein isolation and identification techniques, Dr. Ho studied the CD8 cells of three long-term nonprogressors (people infected with HIV for more than 10 years who still have normal immune systems without any treatment.) The proteins that Dr. Ho's lab identified were initially discovered 20 years ago. They are a group of proteins called alpha-defensin 1, 2 and 3. They were known to kill bacteria by piercing the wall of the bacteria. By using purified alpha-defensin 1, 2, and 3, and antibodies to block them, Dr. Ho's group showed that they appear to be the long-sought-after CAF. This research raises many more questions, such as the potency of these proteins, their potential use clinically, and whether or not these proteins are the cause of some people being long-term nonprogressors. Another interesting fact is that some people naturally have low levels of alpha-defensin 3, so does this help in predicting progression of HIV infection. Other researchers expressed some skepticism prior to Dr. Ho's presentation whether these proteins were the CAF. However, the data presented strongly supported the conclusion that these three proteins are the CAF. (For more details of this presentation, see the review on Medscape (http://www.medscape.com/viewarticle/442254). The site is free but you must register to use it.)

Entry Inhibitors

The newest class of HIV drugs, the entry inhibitors, has been discussed in the last several issues of the *STEP Perspective*. Further analysis of the T-20 (Fuzion®) trials and a report on T-1249 were presented. The T-20 analysis evaluated responses to T-20 in salvage trials where T-20 or placebo was added to a regimen of the best available drugs. This analysis showed that there was a consistent 10-fold decrease (1 log, or about 90%) attributable to the T-20 in all of the subgroups analyzed. These subgroups included gender, ethnicity, baseline viral load, T-cell counts, and number of resistant mutations. What still needs to be presented is the resistance data for T-20. Not everyone responded to T-20 and the company has yet to report which baseline mutations predicted no response to T-20. This is important data so that when T-20 is approved some time this year, a likely cost will be between $12,000 to $15,000 per year, people will know if they might benefit from T-20.

T-1249, also an entry inhibitor, is a slightly different protein than T-20 and needs to be injected only once a day, compared to twice a day for T-20. People who develop resistance to T-20 appear to still respond to T-1249. The results of the Phase I dose escalation study for T-1249 were reported at ICAAC. Doses up to 200 mg were studied and the higher the dose, the more HIV suppression was observed. The only significant adverse effect is the development of tender nodules at the injection site, which is also observed with T-20. In its current formulation, T-1249 contains 50mg/ml. So, a 200mg dose means that patients must receive four separate 1 ml injections to administer each dose. So, while doses above 200 mg were not evaluated in this study, their current formulation would limit the feasibility of using a higher dose.

Once-Daily Drugs

A large international trial compared the newest once-a-day protease inhibi-

continued next page

tor, atazanavir, to Sustiva in people without any prior HIV therapy. All people also received Combivir (AZT and 3TC). There were over 800 people enrolled in this trial. The results of treatment were reported after 48 weeks. The table below shows the HIV levels after 48 weeks.

While the outcome of the two regimens appears similar, there was some concern expressed about the relatively low number of people who have viral loads under 50 after 48 weeks of treatment in the Sustiva group. This is lower than observed in other trials. This may be due to the international nature of this trial (which makes comparisons to other trials difficult), the ethnic composition of this trial, possible differences in drug metabolism, adherence problems (which were not studied in depth in this trial), and/or the different viral load tests that were used during the course of this trial. The major side effect of atazanavir is an elevation in bilirubin, which does not appear to have any clinical significance. The atazanavir group had no elevations of cholesterol or triglyceride, which were observed in the Sustiva group. As reported in the last issue of the *STEP Perspective*, atazanavir resistance occurs through a unique mutation, which may actually result in increased sensitivity of other protease inhibitors. Based on this report and the potential unique resistance pattern, the dose is two pills once a day. Because it causes no elevations in cholesterol or triglycerides, atazanavir will be a very attractive first-line protease inhibitor. FDA approval is expected in the first half of 2003.

Intent-to-treat analysis	Atazanavir	Efavirenz
Number of discontinuations	65 (16%)	79 (20%)
HIV-1 RNA < 400 copies/mL	70% (283/404)	64% (257/401)
HIV-1 RNA < 50 copies/mL	32% (129/404)	37% (148/401)

More progress relating to once-daily regimens was reported at ICAAC. One study compared once-daily Epivir, as a single 300 mg dose, to twice-daily Epivir, as two 150 mg doses, in 554 previously untreated people. All people in this trial also received Retrovir (AZT) and Sustiva. After 48 weeks of treatment, the number of people with HIV-1 RNA levels below 50 copies/mL (by intention-to-treat analysis) were 59% and 61% for the once-daily and twice-daily Epivir arms, respectively. There was no difference in the two arms even when people with high viral loads at baseline were evaluated**.** At the end of June 2002, the FDA approved a change in the labeling for Epivir to allow for once-daily dosing, "The recommended oral dose of Epivir for adults is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents." This change has not been well publicized by the manufacturer, GlaxoSmithKline.

Another once-daily drug, emtricitabine, continues in development. It is similar to Epivir (3TC) and has the same resistance pathway. A study compared emtricitabine to Zerit (d4T), both administered with Videx EC and Sustiva. After 24 weeks, both groups had a similar number of people with viral loads below 50 copies/mL — 81% for emtricitabine, and 70% for Zerit (not a statistically significant difference.) Since Epivir is approved for once-daily administration, it is not clear what advantage the use of emtricitabine offers. STEP would welcome a head-head comparison of these drugs, as it would with Sustiva and Viramune.

Is It Safe to Stop ART if You Started Above Current Treatment Guideline Recommendations?

People who had begun antiretroviral therapy (ART) at higher T-cell counts then current treatment guidelines recommend therapy stopped ART in this study. A total of 49 people were followed in this Spanish observational study begun in 1999. They all had begun ART with T-cells counts between 350 and 500 and HIV RNA loads between 10,000 and 70,000. ART was restarted if the T-cell numbers dropped below 300 or HIV RNA rose to above 70,000 on two measurements. The average time off of treatment was 13.5 months, with a range from 4 months to greater than 3 years. Of concern was that 16 months after restarting ART, the T-cell counts were still lower than when ART was stopped. The rate of T-cell loss during the time off treatment was steady at about 25 cells over 4 months, on average. HIV RNA tended to rise to pre-treatment levels rapidly after stopping ART. In general, this study, and others, show that with close monitoring, it is pretty safe to stop ART if ART was started with higher T-cell counts than current guidelines recommend for starting ART.

HIV Subtypes Show Extensive Recombination

Thomas Quinn presented a lecture reviewing what is currently known about the various subtypes of HIV-1 around the world. There were initially about five major subtypes of HIV-1 identified. The subtypes are referred to by letters, A, B, C, etc. The predominant HIV-1 types differ geographically. Subtype B is the predominant type in North America and Europe, C and A in Southern Africa, and E in Southeast Asia. However, more recent data has now identified subtypes from A to L, with type I actually being a combination of parts of type A, G, H, and K. Cameroon is the country with the most diverse population of subtypes of HIV. There are some potentially clinically relevant concerns about the different subtypes of HIV. The most significant concern is that an effective HIV vaccine

would have to work against many types of HIV, not just the main subtype present in one geographic area. Second, there is some data to suggest that it is easier to transmit subtype C. Third, so far it appears that the subtype present does not affect the response to ART. The implication of most concern, as noted by Dr. Quinn, is that the various recombinations mean that there is a lot of "superinfection", or infection with a second strain of HIV in someone already HIV-infected. This is because the only way for these recombinations to be occurring is for a person to have more than one subtype of HIV in their body.

Prevention and Vaccines for Sexually Transmitted Diseases

Dr. Larry Corey, MD of the Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, presented the first trial ever to show a decrease in transmission of a viral infection with the use of an antiviral medication. This study evaluated the use of an anti-herpes drug, valacyclovir, at 500 mg daily, to a placebo in the prevention of genital herpes. This was a large, multinational trial with 96 study centers. There were 1,494 monogamous, heterosexual couples in which one partner had documented infection with herpes simplex virus type 2 (HSV-2) and the other was HSV-2-seronegative.

The infected partner was treated for 8 months. All the couples also received counseling about how to prevent HSV-2 transmission by use of condoms and abstinence during symptomatic herpes episodes. Symptomatic, laboratory-confirmed genital herpes occurred in 17 (2.3%) of the partners of placebo recipients and 4 (0.5%) of those whose partners were given valacyclovir, a statistically significant difference. There were additional cases documented only by blood test, the infection rates were 3.8% among the partners of placebo recipients and 1.9% in the partners in the valacyclovir group. Similar results were noted whether the infected partner was the man or the woman.

Questions remain about the use of higher doses of valacyclovir. In his review of this study for the Medscape website, Dr. H. Hunter Handsfield, from the University of Washington, writes:

"Despite these uncertainties, in my opinion there is no point in delaying the use of valacyclovir 500 mg once daily to help prevent transmission of genital herpes. Certainly, herpes-discordant monogamous couples, the population directly represented in the study, should be informed of this option (after confirmation of discordance using a type-specific serologic test) and offered treatment. Selected non-monogamous persons also should be offered therapy. Indeed, because most monogamous persons do not contribute importantly to sustained transmission of STDs, any population-based public health benefit in curtailing the HSV-2 epidemic likely will require treatment of infected persons outside monogamous relationships. For the moment, such treatment probably should be restricted to motivated patients who have been carefully counseled about all prevention strategies. Patients must be told that the risk of transmission is reduced but not eliminated; that they must take the medication correctly and consistently; that they still have the ethical responsibility to inform prospective partners that they have genital herpes; and still should use condoms and be alert to symptoms of recurrent herpes and avoid sex when they are present."

There is a lot of "superinfection," or infection with a second strain of HIV in someone already HIV-infected.

A couple of ICAAC sessions reported on progress, or lack thereof, on vaccines for STDs. Progress on development of vaccines for gonorrhea, chlamydia, and genital herpes remains slow. However, progress on a vaccine for human papillomavirus (HPV) is very encouraging. Most people acquire HPV infection in early adolescence. Therefore for people already infected with HIV and HPV, which increases the risk for cervical and anal cancer, a vaccine would be of interest if it could be used to treat HPV after infection has already occurred. However, research into this approach is probably a year or two away.

CORRECTION

In the STEP Perspective, in an article titled "Viread-Videx EC Drug Interactions: What's a Person to Do?" (Volume 02, Number 2, Fall 2002) it was incorrectly stated that the 250 mg dose of Videx (ddI) is not available in the enteric coated preparation. The 250 mg dose of Videx is available as Videx EC. What is not available is the pharmacokinetic (pK) data when this dose is administered with tenofovir to determine if it is the correct dose of Videx EC that should be used with tenofovir.

by Oren Traub, M.D., Ph.D.

Battle of the sexes: gender-based differences in HIV viral load

What is viral load?

In the past decade, the measurement of *viral load*, or the number of copies of HIV virus circulating in the bloodstream, has emerged as a useful complement to the CD4 count in guiding highly-active antiretroviral therapy (HAART). Viral load tends to be high during the initial infection with HIV, but the immune system quickly rallies to suppress replication of the virus, and the viral load drops. However, as HIV infection progresses towards acquired immunodeficiency syndrome (AIDS), CD4 counts drop, and viral load steadily increases.

The earliest studies suggested that the higher the viral load, the quicker the progression to AIDS. With HAART, viral load can be reduced to levels that cannot be detected by laboratory tests. However, viral load increases as HIV becomes resistant to therapy, indicating that a change in medication regimen should be considered for continued suppression of HIV infection.

Measurement of viral load

Viral load is usually measured via a routine blood draw, using a test called reverse transcriptase polymerase chain reaction (RT-PCR). This is a biochemical reaction that amplifies the genetic material (or RNA) of the HIV virus so that it can be measured through special techniques. The standard RT-PCR test can detect no lower than 400 copies of the virus per milliliter of blood, while an ultra-sensitive version of the RT-PCR test can detect as few as 50 copies per milliliter. Currently, the RT-PCR test is the only method that is approved by the Food and Drug Administration (FDA) in the United States to measure viral load

Two other kinds of tests can be used to measure viral load, and are sometimes used in other countries or in clinical trials. One test uses measurement of "branched DNA" (bDNA) to measure viral load and can also detect as few as 50 copies per milliliter of blood. The other test is called "nucleic acid sequence based amplification" (NASBA) and can detect no lower than 100 copies per milliliter. Most people have similar viral load levels when measured by these different methods. However, in some cases, the levels can vary between tests by 2-3-fold. Thus, it is important to use the same method when tracking viral load over time and not to compare results from two different testing methods.

Current use of viral load measurements

The use of viral load in the management of HIV infection is a rapidly changing and controversial field, and current guidelines for its use will almost certainly change in the future. Determination of viral load is most useful when used in conjunction with CD4 counts. While the appearance of opportunistic infections (OIs) seems to correlate better with lower CD4 counts than with increases in viral load, viral load is of use primarily in two situations: early detection of new HIV infection, and determination of the response to medical therapy.

Diagnosis of new HIV infection is confirmed by the detection of antibodies against the HIV virus in an infected individual. However, this antibody may not be present in the bloodstream for up to 6 months, often delaying diagnosis of HIV infection and causing considerable psychological stress. This period of uncertainty is often called the "window period", in which antibody tests may be negative but the virus is actively replicating at high levels within the body. Rather than waiting for the six-month period to pass before re-testing, viral load measurement can confirm active replication of the virus within the body (usually greater than 200,000 copies per milliliter in an early, new infection), thereby establishing or ruling out a diagnosis of HIV infection.

Viral load measurements are also useful in monitoring the response to antiretroviral therapy. While changes in CD4 counts lag after initiation of therapy or changes in medications, changes in the viral load are seen more rapidly and may be a better indicator of the risk of developing OIs. After starting HAART, viral load is expected to decrease by three- to ten-fold over the next four to eight weeks and should be less than 500 copies per milliliter at four to six months, preferably below the range of detection of the laboratory tests. If these levels are achieved, viral load is commonly measured every 3-4 months to determine if the response is sustained. If the viral load does not fall below 500 copies per milliliter at four to six months, treatment is considered to be ineffective and the usual recommendation is to change therapy.

Similarly, if the viral load suddenly increases while on a stable HAART regimen, it may represent emerging HIV resistance to the current drug therapy. However, small variability in viral load between measurements is common (resulting from natural variations in time or from error ranges in laboratory tests) and does not necessarily represent resistance to drug therapy. As a result, a change in viral load of at least three-fold usually occurs before medication changes are considered. Because ten-fold increases in viral load can occur in

the context of vaccinations or any illness (e.g., colds, the "flu", or herpes outbreaks) and persist for one month or more, viral load should not be measured during this time period.

More controversial is the use of viral load in deciding when to initiate therapy. HAART is commonly initiated based on the CD4 count or the appearance of OIs. However, some people advocate starting HAART in asymptomatic people with CD4 counts greater 300 with higher viral loads (>10,000-55,000 copies per milliliter), believing that HIV suppression may be more difficult if viral loads are allowed to increase to even higher levels. While the research regarding this concept is still evolving, use of viral load for this purpose is not currently standard practice.

Gender and viral load

The measurement of viral load clearly has vital importance in assessing the response to drug therapy and determining when medication changes should be implemented. As a result, differences in viral load between different subpopulations, including people of different ethnicities, genders and geographical locations, may have significant implications for the management of HIV infection.

Recent statistics report that women constitute over 50% of the worldwide population living with HIV/AIDS, and the CDC reports that 23% of new AIDS diagnoses occur in women, indicating that women are the fastest growing group with HIV infection. Further, many of the early studies that investigated viral load levels and the use of viral load in the management of HIV included primarily men as research subjects rather than women. Thus, the question was raised: Does the current knowledge regarding viral load and its applications, validated primarily in men, apply to women as well?

Over the past decade, several studies have been performed to investigate that very question. Recently, investigators at the University of California-San Francisco, Johns Hopkins and the National Institutes of Health reviewed these studies and published a combined analysis of their findings. They reported that in seven of the nine cross-sectional (at a specific point in time) studies, women had viral loads that were approximately half that of men. Four other studies were performed in a longitudinal (following people with HIV over time) fashion and found perhaps even larger differences, reporting that women have viral loads that are 50-85% lower than men. These differences held even when accounting for age, race, medications, mode of transmission, CD4 count and time since seroconversion.

Women are the fastest growing group with HIV infection.

Because higher viral loads are associated with quicker progression to AIDS and poorer outcomes, this suggests that women may be able to suppress HIV infection better than men and would seem to be good news for women with HIV infection. Unfortunately, despite these differences in viral load, women progress to AIDS at the same rate as men. As an example, one study reported that the median initial viral load for men who developed AIDS was 77,822 copies per milliliter compared to 17,149 per milliliter for women.

The more alarming interpretation of these results, then, is that women progress to AIDS at much lower viral loads than men. This raises further questions: Should viral load be reduced to even lower levels in women before initial HAART therapy is deemed successful? Should smaller increases in viral load in women on a stable drug regimen be regarded as emerging resistance and trigger medication changes? If men and women progress to AIDS at similar rates, what, truly, is the role of viral load?

While the answers to these questions are lacking, speculation behind the reason for differences in viral load between men and women has already begun. Scientists note that this phenomenon may occur in other viral infections, such as in hepatitis C, where viral load levels are lower in women than in men. Other investigators note that HIV viral levels vary with the menstrual cycle in women and speculate that hormonal influences play a role. This is supported by studies that demonstrate that the cell-surface HIV receptors (CC5R), which facilitate HIV entry into cells, are present in lower numbers in women than in men. Further, in male-to-female transgender subjects who are receiving female hormones, CC5R receptors decrease to levels similar to biological women.

Thus, while the full meaning of lower viral load in women and its implications for the medical management of HIV infections are still unclear, this finding is likely to be a subject of ongoing research, discussion and continuing controversy. If nothing else, this serves as a reminder that clinical studies must include diverse populations and examination of subpopulations in their protocols - because the small differences that gives us our individual characteristics, cultures and personalities may have larger implications for the successful treatment of HIV infection.

by Dr. Shireesha Dhanireddy

Primary HIV infection

Primary HIV infection (PHI) refers to the period of time immediately after initial infection, which is characterized by a prolific phase in viral replication (sometimes up to one million copies of virus) and an acute drop in the CD4 count. However, the HIV antibody is negative, because it has not yet had time to develop. (It usually takes 1-3 months for detectable levels of antibody to HIV to develop.) Identifying individuals during this initial phase of infection is important not only to the newly infected person, but to the community as well.

The most common symptoms of PHI include fever, lymphadenopathy (enlarged "glands"), pharyngitis (sore throat), and rash. These symptoms generally manifest two to four weeks after exposure to HIV. Although PHI often is symptomatic, the symptoms are very nonspecific. A diagnosis of PHI may be overlooked since the symptoms are similar to and at times indistinguishable from the flu or another flu-like illness. Plus, since self-limited, people usually do not seek medical attention during this critical time.

Persons with PHI are, however, thought to be extremely infectious because of the high viral load and high levels of genital shedding found. In one small study, five people with PHI and their partners who subsequently developed PHI were enrolled. The study revealed that HIV is highly transmissible by sexual intercourse during PHI even days before the onset of PHI symptoms. The increased risk of HIV transmission during primary infection is a significant public health concern and emphasizes the need for identifying newly infected persons. However, as noted above, several barriers exist that hinder easy identification of persons during this period of initial infection.

Over the past decade, the trend in HIV care has been to delay initiation of antiretroviral therapy until the CD4 count has dropped significantly. The one exception is persons identified during the period of primary HIV infection. Highly active antiretroviral therapy (HAART) during PHI has produced a shorter symptomatic period and rapid suppression of viral replication. In one study persons with primary HIV infection treated with 2 reverse transcriptase inhibitors and a protease inhibitor had immediate reductions of viral load. Individuals also had significantly decreased incidence of oral and esophageal candidiasis as well as less respiratory complaints.

Persons with primary HIV infection are, however, thought to be extremely infectious because of the high viral load and high levels of genital shedding found.

Treatment during PHI may be protective against rapid progression to AIDS. Bruce Walker and others have shown that HAART for one year may preserve the HIV-specific immune response (your body's ability to fight HIV), leading to long-term "non-progression". Since starting HAART during PHI has not been well studied, once started, it is unclear how long one needs to continue on the medications to have this long-term benefit. One small study by Sarah Fidler and others, presented at the International AIDS Conference this year, found that just a short course of HAART (SCART) after initial HIV infection until the viral load becomes undetectable (4 to 32 weeks) may help keep the immune function against HIV intact. After HAART was stopped, although every participant's viral load rebounded, several people remained at a lower set point. More studies are needed to confirm this, but potentially SCART may reduce the long-term need for HAART, thus minimizing toxicity and costs. Unfortunately, despite the early treatment, however, it has been well documented that the virus is never completely eradicated.

Selecting an initial HAART regimen in primary HIV infection is becoming more and more complicated as viral resistance is increasing. A retrospective study of approximately 200 antiretroviral-naive people revealed increasing drug resistance to non-nucleoside reverse transcriptase inhibitors in primary HIV infection from 0% in the mid-1990's to 8% in 2000-2001. Therefore, resistance testing is now recommended for some newly infected persons who have never been on HAART before, especially in areas of the country with higher rates of resistance. Overall, resistance in antiretroviral-naïve people still remains uncommon, but those persons with drug-resistant infections appear to take longer to virally suppress and have a shorter period of time to drug failure.

It is therefore important to educate both the public and healthcare providers on how to recognize primary HIV infection, to increase the number of people diagnosed during the critical period of initial infection. It is important not only to minimize transmission to others, but appears that treatment during PHI may alter HIV progression over time.

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Andrew Elliott, MD MPH

Depression and HIV
in the Era of HAART

The way that treatment is provided changes the way that people experience chronic illness. In 1997, more effective antiretroviral therapies now called highly active antiretroviral therapy (HAART) became the standard of care for HIV affected individuals. This therapy has changed the face of HIV becoming part of the *language* of HIV infection, its care and treatment. And yet, not all individuals choose or are able to take HAART. When one isn't able to tolerate, manage or choose HAART, he or she may become angry, resentful, or have feelings of failure, helplessness, hopelessness and even depression. Individuals may fail or not be able to take HAART for many reasons including those associated with having few resources, difficulty with adherence, and or mental illness. Because of the way the media has described antiviral therapy for HIV infection, individuals living with HIV are constantly re-evaluating what 'treatment' means to them. Thus, changes in the treatment of HIV/AIDS can affect one's outlook and life perspective. With respect to these new and constantly evolving treatments, one faces many questions. Should I take them and at what point in the course of infection? Are they available to me? What will they do to my life? What will they do to my body? How will I look to others? Will I feel better, or what happens if I feel much better? What if they affect my ability to work? Or will I be unable to tolerate them and then...feel worse?

While these are only a few questions that may arise with new treatments, these thoughts may evoke a myriad of feelings including helplessness, loss of control, rejection, hopelessness, isolation, withdrawal, anger, sadness and fear. These feelings may become what is known as depression or in clinical terms, a major depressive episode. With changes in treatment, many people experience these feelings with the multiple losses of control that occur in the context of HIV infection. One might assume that HIV-infected individuals would 'naturally' become depressed upon learning of their infection or upon the realization that they are unable to tolerate a protease inhibitor. Studies have investigated this, and although there have been no large-scale epidemiological studies, as with many chronic illnesses, this is not the case. Depression in HIV infection is similar to depression in other chronic illness such as heart disease or diabetes.

What is Depression?

The diagnosis of depression is based on a minimal duration of certain symptoms. Major Depressive Disorder (MDD) is diagnosed when one has at least five of the symptoms listed in Table 1 that last for at least 2 weeks. An untreated episode typically gets better within 6 to 12 months. Chronic depression (depressed mood for most of the day, more days than not) that persists for at least 2 years and is not accompanied by the other symptoms listed in Table 1 is diagnosed as dysthymia. Some individuals who have chronic depression (dysthymia) also have intermittent episodes of major depression. This is called "double" depression.

Table 1:
Symptoms of a Major Depression

1. Depressed mood most of the day, nearly every day.
2. Diminished interest or pleasure in all or most activities
3. Increased or decreased sleep nearly every day
4. Fatigue or loss of energy nearly every day
5. Loss of appetite or weight
6. Insomnia or increased sleep
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Decreased ability to concentrate
9. Agitation
10. Recurrent thoughts of death or suicide or suicide attempt
11. Feelings of hopelessness

Adapted from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th edition. Washington, DC: American Psychiatric Press 1994:327.

Depression and HIV infection

Cross-sectional and prospective studies in HIV-positive populations estimate the lifetime prevalence of depressive disorders ranges from 22% to 35% and the current prevalence (1-2 months) ranges from 6% to 10%. These rates are all el-

evated when compared to the estimates of lifetime (9%) and current (3%) prevalence of major depression in the general community. Depression appears to be the most common psychiatric disorder found among HIV-infected individuals. Similar to HIV infected persons, people who are HIV- negative, but at-risk for HIV infection, have similar increases in rates of depression. In other words, if you are from a population that is at-risk for HIV infection, you are also at increased risk of depression compared to the general population.

Table 2:
Risk factors for Major Depression in HIV+ or at-risk populations

- Family history of history of depression
- Alcohol, IV drug or other substance use
- Loss of social supports
- Multiple losses
- Advanced HIV infection

Depression has a significant effect on quality of life, progression of disability and ability to receive good medical care. With the development of HAART, which has the potential to manage HIV infection and prolong life, treatment of depression is even more important, since untreated depression could both compromise medication adherence leading to viral resistance and also potentiate the disabling effects of the illness.

It was initially suggested that HIV itself causes depression, that HIV associated neurocognitive changes (now referred to as HIV Associated Cognitive Impairment) may be a cause of depression or that HIV associated medications may cause mood changes. There are a few case reports that address these issues, but there is very little evidence to support any of these hypotheses. Depression has a biological and neurochemical basis in the context of an individual's social functioning. From the opposite standpoint, many reports have investigated whether depression leads to HIV illness progression with a decline in the CD4 count and increase in the viral load. While viral load studies haven't been reported for large populations, these reports all seem to indicate that depression is not associated with progression of illness. Other lymphocyte markers such as natural killer cells or CD16 cells may be more associated with stress, depression and coping, but these need to be further studied. Recent reports suggest such associations.

Many depressive symptoms are difficult to assess in individuals with chronic illness. Chronic illness may generate symptoms that look like depression and depression can mimic symptoms of a medical illness. Identification of physical symptoms (associated with medical illness) or psychological symptoms (anxiety or loss of interest in activities when bedridden, housebound, or unable to participate in social and recreational activities) is important. In the early stages of HIV infection, these symptoms rarely coexist with true depression, however, as HIV infection progresses, physical symptoms attributable to HIV itself are difficult to separate from the symptoms of a depressive disorder. In these cases, it is important to rule out a physical illness first. Then, your healthcare provider should review the symptoms present and consider the most prominent ones. When other causes have been ruled out, depressed mood is most often the prominent symptom.

Table 3:
Medical Symptoms Mimic Depression

If you have any clusters of medical symptoms that include but are not limited to the following you may want to talk with your primary care provider about depression

- Shortness of breath, lethargy, fever cough
- Headache, depression, social withdrawal
- Chronic pain or pain in your arms or legs
- Headache, insomnia, difficulty concentrating
- Memory loss, social withdrawal, feeling confused
- Withdrawal, isolating, changes in feeling in your hands, legs or problems walking or moving
- Suspiciousness, anxiety, bizarre or obsessive thoughts

Treatment of Depression in HIV infection ™

Many treatment options are available. If you are experiencing any or some of symptoms listed in Table 1, you should consider seeking further evaluation and treatment via a mental health provider or your primary care provider. The most effective methods of treating depression include a combination of counseling (psychotherapy) and medication. Psychiatrists, psychologists, nurse practitioners, and social workers all provide different forms of treatment for depressive disorders.

Psychotherapy

Psychotherapy or counseling in HIV-positive individuals has been approached using several models including supportive therapy, interpersonal therapy (IPT), cognitive behavioral therapy (CBT), biofeedback, stress-reduction/relaxation exercises, alternative therapy, and group therapy. Common themes for people during therapy are loss of relationships and autonomy, loss of employment, declining physical well-being and appearance, fear of neurologic problems, loss of spirituality as well as fear of stigma and discrimination.

All forms of therapy involve supportive elements that play a role in the success of the therapy, but supportive and insight-oriented therapy define support

as paramount. Not only is the supportive relationship between therapist and patient a vehicle for exchange of information between patient and therapist, but the relationship itself is of therapeutic benefit in a variety of ways.

IPT has been studied in outpatient HIV-positive individuals with MDD. For these people, IPT helped them relate changes in mood to changes in their environment or in role changes. The therapist engages the client in their emotional life issues, conceptualizing difficulties within one of four interpersonal problem areas: grief, role dispute, role transition, or interpersonal deficits. The therapist then uses specific strategies to deal with the problem areas, focusing on the here and now, on what the patient wants to achieve, and on what options exist to achieve it.

Table 4: Treatment Options

PSYCHOTHERAPY
- Supportive
- Interpersonal
- Cognitive-Behavioral
- Biofeedback
- Stress-Reduction
- Alternative Therapies
- Group

PHARMACOTHERAPY
- Antidepressants
- Stimulants
- Testosterone

COMBINATION THERAPY
- Psychotherapy + Medications

In contrast, CBT is based on the philosophy that depressed people distort reality in a particularly negative way. CBT involves setting goals, defining target symptoms, problem solving, and investigating relationships between thoughts and emotions and their underlying assumptions. In the context of CBT, self-defeating behaviors and interpersonal and coping skills are often addressed. For example, a CBT therapist would challenge a HIV-positive client's view that their life is hopeless. The goal is to help the client believe that people have the capacity to construct a positive sense of the future. The CBT therapist would engage the client in an effort to identify hypotheses that would support or reject their beliefs.

Group therapy has been used extensively with HIV-positive individuals in a variety of contexts and is highly efficient. Sessions provide psychoeducation, confrontation regarding misperceptions about the illness, and shared experiences, all of which help to improve patients' mood and quality of life.

The goal of counseling should be to help individuals to function as well as they can. Therapists should try to adapt the psychotherapy method they are most comfortable with the special needs of the person living with HIV. People living with HIV are not significantly different from other clients. The therapist should provide an objective but empathic environment where the individual can freely express their emotions. Therapy should attempt to engage clients in assessment and mobilization of their resources, including those provided by family, friends, and community. Psychoeducation should be provided about HIV, its course, treatment and effects.

Pharmacotherapy

The approach to pharmacotherapy for HIV-positive individuals with a depressive disorder may be slightly different than for the general adult population. HIV-positive individuals often respond differently to medications, often being more sensitive to them, and may need a "start low and go slow" approach. In addition, individuals with advanced HIV infection are often on multiple medications which increases the probability of drug-drug interactions and the chance of experiencing side effects. More recent studies have called attention to the important relationship between tolerability and efficacy in this population.

MDD in patients with HIV infection has been effectively treated in open trials with almost all antidepressant medications. Of these, only three (imipramine, fluoxetine and paroxetine) have been investigated in randomized placebo-controlled trials. Imipramine demonstrated an effective antidepressant response that was similar to that seen in medically healthy depressed patients. The efficacy of fluoxetine appears similar to that of desipramine, sertraline and paroxetine. When compared to tricyclic antidepressant, fluoxetine, paroxetine, sertraline, and citalopram (known as "SSRIs") are more tolerable and have fewer side effects, which may lead to an increased overall effectiveness.

Testosterone replacement has been shown to improve depressive symptoms in individuals with low testosterone levels, especially for those with decreased libido or sexual dysfunction. Before testosterone is administered, a patient's testosterone levels should be checked.

Additionally, stimulants have been shown to improve mood, energy and alertness and have been shown to be effective in medically ill populations. Several open trials that used stimulants have suggested that people benefit from them with a decrease in depressive symptoms and an improvement in cognitive deficits. It is important to note that stimulants have side effects that include insomnia, agitation, weight loss and paranoid ideation, plus tolerance may develop after initial benefit. There have yet to be significant randomized, placebo-controlled trials that more thoroughly evaluate stimulants against other antidepressants with respect to tolerability and overall efficacy.

Side effects and tolerability are important aspects to treatment in the HIV-positive person. People may have many concerns about medications including loss of control, the ability to distinguish symptoms that may indicate physical illness, increase or change in weight, sedation, and sexual dysfunction. All of these side effects can affect how a per-

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Depression and HIV

continued from previous page

son tolerates a medication. The provider initiating antidepressant treatment should consider the individual's HIV-related symptoms when selecting an antidepressant. Tricyclic antidepressants (TCAs) may be more sedating and therefore may be helpful for insomnia. On the other hand, the anticholinergic side effects (the side effects due to blocking a branch of the nervous system) may actually be helpful for managing chronic diarrhea, concurrent neuropathy or neuropathic pain. SSRI antidepressants are not usually sedating and can cause nausea, exacerbate chronic diarrhea or have sexual side effects, but may alleviate chronic constipation. Stimulants may increase cognitive processing, but can cause agitation and weight loss.

The newer antidepressants including citalopram, venlafaxine, nefazodone, and mirtazapine have all been investigated in open (non randomized, non blinded) trials. They have different side-effect profiles from the TCA's and SSRIs and may be especially helpful in people who cannot tolerate these other classes of antidepressants. Venlafaxine has properties of both TCAs and SSRIs, but side effects are avoided at low doses. Nefazodone has no reported sexual side effects and although it is known to cause dry mouth, and dizziness upon initiation of therapy, these symptoms are often easily tolerated and resolve. Mirtazapine may be useful in patients who are experiencing insomnia and need to gain weight. These newer antidepressants, as with both the TCAs and SSRIs, all need to be evaluated in the context of the individual's current HIV-related symptoms and how they are affecting their quality of life.

In general, SSRIs and the newer antidepressant medications have several advantages over TCAs for patients with HIV illness. These drugs are likely to be better tolerated with fewer side effects leading to a lower incidence of side-effect related dropout and increased compliance with treatment and as a result are likely to be more effective in treating depression. They are not sedating and do not have the anticholinergic side effects seen with TCAs. Therapeutic dosing is easier, as well, often allowing management by the primary care provider.

Table 5: Types/Classes of Antidepressant Medications

Tricyclics: Amitriptyline, Nortriptyline Desipramine, Imipramine

Second Generation: Venlafaxine, Mirtazapine, Bupropion, Nefazodone

SSRI's: Paroxetine, Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram

MAOI's: Parnate, Nardil

Other: Trazadone

Stimulants: Methylphenidate, Dextroamphetamine

Clients should be educated about the length of time it takes for antidepressant response (often 3 to 4 weeks) and about common side effects they might experience with a particular antidepressant and how this may affect their HIV illness. And finally, it is especially important for individuals to reinforce compliance by arranging contact with their health care provider within a brief time after initiation of therapy in order to evaluate side effects, treatment effect, and expectations.

Protease Inhibitors & Anti-depressants

Of the FDA approved protease inhibitors, ritonivir (Norvir) may be the most potent inhibitor of the drug metabolizing system referred to as the cytochrome P-450 system. It is a collection of enzymes which metabolize many of the natural chemical and medications in your body. Many HIV-related medications inhibit these enzymes including ketoconazole, clarithromycin and the protease inhibitors. The protease inhibitors are known to inhibit specific a specific group of enzymes referred to as the 3A group. While ritonivir and indinavir are known to potently inhibit the 3A system, not all protease inhibitors have the same specificity for the these systems. Several antidepressants are metabolized through one or more of the cytochrome P-450 enzymes including fluoxetine, fluvoxamine, paroxetine, citalopram, nefazodone, and tricyclic antidepressants. Levels of the antidepressant which are metabolized by the 3A system may be increased when protease inhibitors are administered concurrently which in turn are experienced by the patient as side effects and may be misinterpreted as a change in medical illness state and lead to medical evaluation or hospitalization. Patients at increased risk of drug interactions include those who are on multiple medications with multiple medical illnesses, those with deficiencies in one or more cytochrome P-450 enzyme systems, those with renal and hepatic disease, those who are elderly and or physically debilitated, and those who are on a single potent enzyme inhibitor such as a protease inhibitor. Prescribing providers should carefully evaluate patients on protease inhibitors for possible drug interactions and side effects.

Approach to Pharmacotherapy with Anti-Depressants in HIV infection

- Investigate causes of medical illness that may present as depressive symptoms.
- Review all currently prescribed medications. Evaluate for any possible drug-drug interactions.
- Address issues of alcohol and substance abuse/dependence.
- Consider tolerability and adherence to medications (e.g. sensitivity to side effects).
- Selective serotonin reuptake inhibitors (SSRIs) or newer generation antidepressants (citalopram, mirtazapine, venlafaxine, nefazodone) with fewer side effects may provide equal efficacy and increased tolerability as compared to older antidepressants (TCAs).
- The presence of depression and neuropathy may indicate the use of TCAs as these may augment neuropathic symptoms.
- The presence of depression and weight loss may indicate use of mirtazapine (Remeron) which both stimulates appetite and increases weight.
- In advanced HIV infection, as in other chronic illnesses, stimulants may improve mood, energy, an alertness and cognitive ability.
- Additionally, for those patient with low testosterone levels, testosterone replacement may improve depressive symptoms.
- Educate the patient about the course of depression, treatment response, and side effects.
- History of previous depression and treatment resistance may suggest maintenance therapy.

by Barb Falkner, BSc(Pharm) and Bradley Kosel, PharmD

Methadone and HIV Medications

Drug Interactions

Who needs to care?

Injection drug use is a risk behavior that may result in acquired immunodeficiency syndrome (AIDS). Treatment for substance abuse may be an important part of AIDS prevention and treatment. Methadone is a medication used as a substitute for heroin or other morphine-like drugs. Supportive services are usually included as part of the methadone treatment. Generally the dose is given orally once a day. Medications used to treat HIV may be used concurrently with methadone.

Methadone can interact with other medications. A drug interaction occurs when one drug changes the effects of another drug. Sometimes the drug interaction is too small to make a difference, other times it may cause problems. For example, a medication may reduce the effects of methadone and lead to symptoms of narcotic withdrawal or increase the effects of methadone and cause increased sleepiness. It can also work the opposite way. Methadone may work the same, but it may increase or decrease the effects of other medications. HIV medications may not work as well, or their blood levels may be elevated and cause unnecessary side effects. The dosages of medications (both methadone and HIV medications) can be adjusted to account for the predicted drug interactions to provide optimal therapy. For example, if the antiretrovirals (ARVs) are causing too many side effects when methadone is started or visa versa, ARVs can be safely adjusted, depending on symptoms and blood tests. There is no need to supplement methadone with heroin, stop antiretroviral medication, or stop other HIV-related medications. Stopping or missing doses of antiretroviral medications can lead to ineffective treatment and/or the development of resistance. It is important for people using methadone to let their healthcare providers know if they suspect a drug interaction.

Highlights of Potential Interactions

Metabolism is how the body eliminates drugs. This occurs mainly through the liver and the kidneys.

Hepatic metabolism is done by the liver. There are three ways drugs can interact with liver metabolism.

• **Substrate interactions**. The liver can do only a limited amount of metabolism at once. When two (or more) drugs are taken at once that need the liver for metabolism, they can compete for specific enzymes in the liver. This can affect the extent to which drugs are metabolized.

• **Induction interactions**. Induction occurs when a medication causes the liver to metabolize certain drugs faster than usual. It takes about 2 weeks for the effects of the induction to fully take place. This may result in decreased blood levels of medications, which may make them less effective.

· **Inhibition interactions**. Inhibition occurs when a medication causes the liver to metabolize certain drugs more slowly than usual. One drug inhibits the metabolism of another drug, so there are extra amounts of that drug around. This can lead to toxic effects. Inhibition can occur soon after the drug is ingested.

Renal excretion is done by the kidneys. This is another way the body eliminates drugs. Methadone is eventually excreted renally, but it usually does not interact with other drugs that are renally excreted.

"General Rules"

There are "general rules" about how groups of drugs are metabolized, and being aware of the rulesmakes it easier to understand specific interactions. The generalrules are as follows:

• All of these interactions may occur when either methadone is started or stopped, or when other medications are started or stopped. The exact amount of time for these interactions to occur varies between people and depends on a number of factors, such as how long they have received methadone, how well their liver is working, what other medical conditions they have, and whether the interaction is induction (about 2 weeks) or inhibition (immediate or within a couple days).

• The liver metabolizes methadone and it tends to interact only with other drugs that are metabolized by the liver.

·Most of the nucleoside reverse transcriptase inhibitors (NRTIs) undergo renal excretion, so they do not interact with methadone. However, there are

two exceptions, zidovudine and abacavir. But only abacavir may require a methadone dosage adjustment.

• All of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by the liver. They may interact with methadone and require a methadone dose adjustment.

•The protease inhibitors (PIs) are metabolized by the liver. The only PI that may require a methadone dosage adjustment is ritonavir.

• Any type of liver disease (e.g., hepatitis C, alcoholic hepatitis) may make these interactions more pronounced, because the liver may not work as well.

What specific drugs interact?

Everyone is different. Some people may have these interactions and other people may not. The effect of these interactions may be too small to require a dose adjustment for some people, but other people may need dosage adjustments, and even have to use different medications. When these interactions occur it will be different for each person because everyone's metabolism is a little different. Also, people react differently to medications as their bodies adjust to the effects. Table 1 shows the most important drug interactions. Many drug interactions are unknown. This means there aren't enough studies completed to effectively determine what will happen.

Methadone and Antiretroviral Medications – Highlights of Potential Interactions

• Zidovudine (AZT), didanosine (ddI) and/or stavudine (d4T) effects maychange with methadone. The effect and dose of methadone remain the same. Usually the doses of AZT, ddI, and d4T remain the same.

• Abacavir, nevirapine, efavirenz, and ritonavir, may reduce the effectiveness of methadone and an increase in the methadone dose may be required. Again this will not happen in every patient, and because this is induction, the effect usually takes about 2 weeks to occur. Whenever there is potential for decreased methadone levels, withdrawal symptoms may be present.

• Nelfinavir may reduce methadone levels, but the effect is usually not felt and the methadone dose remains the same. Withdrawal symptoms are not likely.

Table 1 Potential Methadone Drug Interactions

Medication	Effect on Methadone	Effect on HIV-Related Medication	Potential Significance / Recommendation
NRTI			
Zidovudine (Retrovir®, AZT. 3TC)	None	**May** increase AZT	No dose adjustments Watch for signs / symptoms of AZT-adverse effects (e.g., headache, muscle aches, fatigue, irritability)
Didanosine (Videx®, ddI)	None	**May** decrease ddI	No dose adjustments Monitor CD4 and viral load to ensure ddI is working.
Zalcitabine (ddC)	Unknown	Unknown	Unknown
Stavudine (Zerit®, d4T)	None	May decrease d4T	No dose adjustments Monitor CD4 and viral load to ensure d4T is working.
Lamivudine (Epivir®, 3TC)	None	Unknown	Unknown
Abacavir (Ziagen®, ABC)	**May** increase methadone clearance (i.e., it may leave the body faster than before)	**May** increase the time it takes abacavir to be absorbed.	Monitor for signs/symptoms of withdrawal.
AZT/3TC/Abacavir (Trizivir®)	Unknown	Unknown	Unknown
NTRI			
Tenofovir (PMPA)	Unknown	Unknown	Unknown
NNRTI			
Nevirapine (Viramune ®)	**May** decrease methadone levels	Unknown	**May** need increased methadone dose
Delavirdine (Rescriptor®)	**May** increase methadone levels (predicted)	Unknown	**May** need decreased methadone dose
Efavirenz (Sustiva®)	**May** decrease methadone levels	Unknown	**May** need increased methadone dose

Table 1 continued, next page

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Medication	Effect on Methadone	Effect on HIV-Related Medication	Potential Significance / Recommendation
PI			
Indinavir (Crixivan®)	Unknown	Unknown	Unknown
Ritonavir (Norvir®)	**May** decrease methadone levels	Unknown	**May** need increased methadone dose
Nelfinavir (Viracept®)	**May** decrease methadone levels	No	Methadone dose usually stays the same
Saquinavir (Fortovase®)	Unknown	Unknown	Unknown
Amprenavir (Agenerase®)	Unknown	Unknown	Unknown
Lopinavir (Keletra®)	Unknown, but contains ritonavir so may decrease methadone levels	Unknown	Unknown
Combination of Ritonavir and Saquinavir used together	**May** increase the metabolism of inactive S-isomer of methadone; because this is the inactive isomer, the effect on the patient is usually nothing.	Unknown	Methadone dose usually stays the same

Table modified from the following:

1.Gourevitch MN, Friedland GH. Interactions between methadone and medications used to treat HIV infection: a review. *The Mount Sinai Journal of Medicine* 2000;67:429-436

2.College of Pharmacists of British Columbia Bulletin. 2001;26:8.

3. Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD: John Hopkins University; 2001.

4.Gerber JG, Rosenkranz S, et al. Effect of ritonavir/saquinavir on stereoselective pharmacokinetics of methadone: results of AIDS clinical trials group (ACTG) 401. *JAIDS* 2001;27:153-160.

Conclusion

The bottom line is that people taking methadone need to be aware of the **possibility** of interactions with any of the following medications: nevirapine, efavirenz, ritonavir, nelfinavir, lopinavir/ritonavir. Also, the time it takes for drug interactions to occur is different depending on the person and the drugs involved. People with concerns or questions should talk to their pharmacist or healthcare provider to have the dose of either methadone or the other medications changed. Together, optimal therapy for both methadone maintenance and HIV medications can be worked out.

A Novel Strategy Study Opens at the ACTU

A5073: A Randomized, Phase II, Open Label Study to Compare Twice-Daily and Once-Daily Potent Antiretroviral Therapy and to Compare Self-Administered Therapy and Therapy Administered Under Direct Observation

The UW AIDS Clinical Trials Unit is enrolling volunteers for a major new treatment strategy trial. The study will look at two different treatment strategies in people who have not taken HIV medications previously. The study will compare once-a-day versus twice-a-day administration of the same drugs, and also compare directly observed therapy (DOT) to self-administration in the group receiving once-daily therapy. The drugs used in this study will be Kaletra, the new, extended-release formulation of Zerit (d4T), and FTC, a new once-a-day NRTI. A total of 375 people will be enrolled nationally on this study.

All participants will be randomized into one of three groups to take anti-HIV medications once or twice a day, and the once-a-day group will be randomized into DOT versus self-administration. Those randomized into the DOT group will be required to visit the clinic every day (Monday through Friday) to receive their medications for the first 24 weeks (or possibly to meet a study nurse at a convenient location). The other participants will self-administer medications and will visit the clinic every 2 weeks for the first 16 weeks of the study, and every 8 weeks thereafter, for a total of 48 weeks. There is a 20 percent probability (a 1 out of 5 chance) of being randomized into the DOT group.

Medications, viral load counts, and CD4 counts are provided by the study. All participants are reimbursed $20 per visit when lab work is done. Participants randomized into the DOT group also get $5 for each day of DOT.

Potential participants need to meet the following criteria: they should be HIV-positive; have no prior use of HIV medications; be at least 13 year of age; have a viral load greater than 2000; have no severe medical conditions or infections; and, if female, not be pregnant or breastfeeding.

For more information, call Alyssa Spingola or Lori Cray at 206-731-3184 or email the ACTU at:

actu@u.washington.edu.

By Jeffrey Schouten, Community Representative to the AMC

AIDS Malignancy Consortium Opens

Major New HIV Lymphoma Trial

The AIDS Malignancy Consortium (AMC) is a group of 15 major medical centers that conduct research for the treatment of HIV-related cancers. The group is funded by the National Cancer Institute (NCI.) The two most common cancers seen in people with HIV are Kaposi's Sarcoma (KS) and lymphoma.

KS is an abnormal growth of blood vessels associated with a herpes-type virus, KS-HV, which most commonly appears on the skin. With current antiretroviral therapy (ART) the incidence of KS has declined dramatically, but still remains a problem for many people. The AMC has several KS trials ongoing.

Lymphoma is a cancer of the lymph nodes. The most common type seen in people with HIV is non-Hodgkin's lymphoma (NHL) is also occurring. Historically, Hodgkin's Lymphoma has a higher cure rate with chemotherapy than does NHL. With current ART, the incidence of lymphoma is declining, but not as much as the declines seen in KS. Fortunately, one of the most aggressive lymphomas, that of the brain, also known as CNS lymphoma, has declined dramatically with ART. The AMC has been unable to enroll enough people in their current CNS lymphoma trial due to the declining incidence of this type of lymphoma. Also, there has been a decline in some of the more aggressive lymphomas, the immunoblastic type, with ART. Declines in other types of HIV-associated lymphomas have not been as great. Thus, there remains an ongoing need for clinical research into the treatment of HIV-associated lymphomas.

The AMC has just completed a large NHL trial, enrolling over 150 people. This trial, number 010, is being analyzed and results will be available next spring. The 010 trial compared the standard chemotherapy regimen, CHOP, with CHOP plus a monoclonal antibody which attacks lymphoma cells, rituximab. Rituximab attacks a site on the surface of lymphocytes known as CD20. Most HIV-associated lymphomas have CD20 present on the lymphoma cell surfaces. Rituximab plus CHOP has been shown to be better than CHOP alone, in people with lymphoma who are HIV-negative.

The next AMC lymphoma trial just starting is trial 034. This trial will study a chemotherapy regimen that is probably more potent than CHOP, but needs to be given as a four-day continuous infusion, every 3 weeks, for 2-6 cycles, depending on response. The regimen is known as EPOCH. The study will ask if the results of treatment are better is rituximab is given with the EPOCH or afterwards. A total of 70 people will be enrolled in this trial. A trial conducted by the NCI of a similar infusional regimen, CDE, showed very high response rates, with few relapses in HIV-associated NHL. In the NCI study, all anti-HIV drug treatment was stopped during the chemotherapy treatment period because of concerns over possible drug interactions. However, the AMC 034 trial will allow trial participants and their health care providers decide whether or not to continue ART during the chemotherapy treatment period.

There is a local AMC Unit at Virginia Mason Medical Center, headed by Dr. David Aboulafia, and a subunit at Harborview's Madison Clinic. For information about this, or other AMC trials, you can call Cheryl Weaver, Study Coordinator, at 206-223-6835. Also, information about ongoing AMC trials is available at their website: http://www.amc.uab.edu/.

University of Washington AIDS Clinical Trials Unit—Open Winter 2003

206-731-3184 **http://depts.washington.edu/actu** **actu@u.washington/edu**

Complications of HIV & Other Conditions Studies

Study # 5082 **Lowering blood insulin and body fat** **Length: 32 weeks (about 8 months)**

- **Treatment:** Metformin & Rosiglitazone **or** Metformin placebo & Rosiglitazone **or** Metformin & Rosiglitazone placebo **or** Metformin placebo & Rosiglitazone placebo
- **Eligibility:** •HIV+ • age 18-65 • Increased waist size • HIV RNA (viral load) less 10,000 • on stable ARV and not planning to change • No prior use of anti-diabetic medications.
- **Compensation:** $25 paid for each CT or DEXA scan and $20 for each study visit.

Study # 5090 **HIV-associated Dementia** **Length: 24 weeks with optional 24 wk extension**

- **Treatment:** Selegiline Transdermal System (STS patch) vs OR STS patch placebo
- **Eligibility:** • HIV+ •Age 18+ • Males and non-pregnant females • Documented HIV dementia • on stable ARV drugs e more than 8 weeks • No current mental illness.
- **Compensation:** All subjects offered STS at 24th week. $20-100 paid for some tests

Study # 5084
Evaluation Of Metabolic Complications Associated with Antiretroviral Medications in HIV-1-infected Pregnant Women **Length: 38 weeks**

- **Treatment:** Anti-HIV medications will not be not be provided on this study
- **Eligibility:** •HIV+ • Taking PIs 8 weeks prior to study entry or not taking a PI 8 weeks prior to study entry Between 20-34 weeks pregnant •No history of diabetes (except prior history of diabetes during pregnancy) •13 years of age or older • No major fetal anomaly as diagnosed by ultrasound • No major complications during current pregnancy.
- **Compensation:** $20 for visits/exams and lab tests given at no cost.

Study # 5092 **Drug-drug interactions in HCV** **Length: Approx 8 weeks**

- **Treatment:** Ribavirin prescribed by other health care provider
- **Eligibility:** •HIV+ •HCV+ •13+ years of age •CD4 >100 •On AZT or d4T at least 4 weeks prior to entry •Planning to start Ribavirin •No Ribavirin for at least 6 months prior to entry
- **Compensation:** $150 paid for each of 2 10-hour clinic visits (one at entry, and another at week 8)

Study # 736 **HIV in cerebrospinal fluid** **Length: 48 weeks**

- **Treatment:** None
- **Eligibility:** •CD4 cell count 200 or less cells/mm3 • HIV RNA 2000+ copies/ml or HIV RNA 50,000+ with any CD4 count •Starting or changing antiretroviral therapy
- **Compensation:** $100-$125 for each lumbar puncture (3)

Study # 079 **HIV in the lungs** **Length: 1-2 visits**

- **Treatment:** None
- **Eligibility:** •HIV positive •HIV RNA >50 copies/mL
- **Compensation:** $25 for sputum sample

Physicians or potential participants can call Alyssa or Loni at 206-731-3184 for information or appointments. Screening tests, study medications, laboratory, and clinical monitoring that are part of a study are provided free of charge.

Antiretroviral Studies Open to Enrollment-Winter 2003

Study # 5073 **Comparing Twice Daily & Once Daily and comparing Self-Administered Therapy and Direct Observation Therapy**
Length: 1year

- **Treatment: Group # 1** LPV/r + FTC + d4t twice a day (almost all doses taken outside the clinic) **Group # 2** LPV/r + FTC + d4t once a day (almost all doses taken outside the clinic **Group # 3** LPV/r + FTC + d4t once a day (almost all doses observed by a health care worker)
- **Eligibility:** •HIV+ %age 13+ •Viral load e •2000 %No prior antiretrovirals •No severe Medical Conditions •Men & non-pregnant women
- **Compensation:** $20 per study visit plus $5 for DOT meeting

Study # 5029 **New!!** **HPV and HIV in ARV-inexperienced women** **Length: 3-5 years**

- **Treatment: None.** ARV (Antiretroviral therapy) prescribed by another physician or primary health care provider
- **Eligibility:** •HIV infection •age 13+ •Have taken no anti-HIV meds in the past but now starting •Must not have had cervical cancer in the past
- **Compensation:** $20 for study visit. Study includes brief pelvic exams, pap smears, and blood draws. Subjects with abnormal pap smears will have a colposcopy.

Study # 5043 **Drug Levels in HIV-Negative persons** **Length: 6 wks/3 wks on drugs**

- **Treatment:** Efavirenz for 10 days; Add APV for 3 days; Add a third drug (IDV, NFV, RTV, or SQV) for 1 week in 80% of enrollees
- **Eligibility:** •HIV- •18-65 years •Males; females not able to become pregnant •No chronic illnesses •No chronic medications
- **Compensation:** 3 inpatient visits plus follow-up visit reimbursed at $150 each

Study # 5143 **LPV/r & GW433908 alone or together in addition to TDF + 1 or 2 NRTIs** **Length: 1year**

- **Treatment:** •LPV/r + TDF +1 or 2 NRTIs **OR** GW433908 + RTV+ TDF+ 1or 2 NRTIs **OR** LPV/r + GW433908 + TDF + 1 or 2 NRTIs
- **Eligibility:** •HIV+ •18+ years of age •use of at least 1 PI-containing regimen for 12 weeks min. that has changed or will due to virological failure or detectable plasma HIV-1RNA **%** min 1 year anti-HIV drug experience •HIV RNA >5000 copies/mL •Non-pregnant or breast feeding females •No prior use of lopinavir or amprenavir
- **Compensation:** $10 per study visit; $100 for sub-study visit.

Study # 5093 **Effects of ARVs on Depo Provera** **Length: 12 wks**

- **Treatment:** **Will receive one injection of Depo-Provera • No ARVs provided by study.**
- **Eligibility:** •HIV+ women •age 13+ years • On **no** ARVs and CD4 >200 •On EFV, NVP, NFV, or IDV/RTV and CD4 >350 •HIV RNA <10,000
- **Compensation:** 2 inpatient visits for most subjects-provides reimbursement

Key to terms

3TC: lamivudine (Epivir)
ABC: abacavir (Ziagen)
APV: amprenavir (Agenerase)
AZT: zidovudine (Retrovir)
ddI: didanosine (Videx)
SQV: saquinavir (Invirase)
NVP: nevirapine (Viramune)
d4t: stavudine (Zerit)
ddC: zalcitabine (Hivid)
E**FV**: efavirenz (Sustiva)
RBV: Ribavirin
NFV: nelfinavir (Viracept)
RTV: ritonavir (Norvir)
IDV: indinavir (Crixivan)
NRTI: Nucleoside Reverse Transcriptase Inhibitor
PI: Protease Inhibitor
HAART: Highly Active Antiretroviral Therapy
ARV: Antiretroviral
NNRTI: non-nucleoside reverse transcriptase inhibitor
LPV/R: lopinavir/ritonavir (Kaletra)
TDF: Tenofovir

Ask Dr. Jeff

by Dr Jeff Schouten

Q: *I have heard that people with weak immune systems could get very sick, or die, if exposed to people who have received the smallpox vaccine. Is this true?*

A: The smallpox vaccine is a live virus vaccine called vaccinia. Anyone with a weakened immune system could have a potentially fatal infection from live virus vaccines. In fact, even in people with a normal immune system, there is a risk of death from the smallpox vaccine estimated to be 1-2 deaths /1 million vaccinations. Additionally, the risk of healthy people developing a disseminated vaccinia virus infection, called eczema vaccinatum (EV), a very serious condition, is thought to be about 10-39 people / 1 million vaccinations. People with a diagnosis or history of eczema, or atopic dermatitis, are much more likely to develop EV.

According to the Centers for Disease Control (CDC), following vaccination, "a red and itchy bump will develop at the vaccine site in three or four days. In a week, the bump becomes a large blister and fills with pus and begins to drain. During week two, the blister begins to dry up and a scab forms. The scab falls off in the third week, leaving a small scar. People who are being vaccinated for the first time have a stronger reaction than those who are being revaccinated." Live vaccinia virus is present at the vaccination site until the dry scab forms.

There is some risk of transmission of vaccinia virus from a vaccinated person to an unvaccinated person, also referred to as contact vaccinia (CV). John Neff, and colleagues, from Children's Medical Center in Seattle, recently studied this transmission risk, as reported in an article in the Journal of the American Medical Association (JAMA) on October 16, 2002. Most of the reported cases of CV occurred in close household contacts. The risk was found to be about 2-6 cases / 100,000 vaccinations. The risk of EV was 1-2 cases / 100,000 vaccinations. However, these studies are based on transmission rates observed in the 1950's and 1960's. At that time HIV was not known to exist, not many people were immunosupressed because of organ transplants, not as many people were receiving chemotherapy for cancer, immune-suppressing steroids were used less frequently, and the incidence of eczema in the population was much lower than it is today. These factors would suggest that today there is a much larger pool of people at risk of developing EV if they acquired vaccinia from a person vaccinated. People who have household or intimate contacts who have a weakened immune system, are pregnant, or have any of the above skin conditions should not be vaccinated. This is due to the risk of transmitting vaccinia virus to their close contacts.

What about the risks of a vaccinated health care worker infecting a person with HIV?

In general the reaction to the vaccine is limited to the injection site and with a sterile dressing over that site, and proper hand washing techniques, there probably is little risk of a health care worker transmitting vaccinia to a patient. The Advisory Committee on Immunization Practices (ACIP) October 2002 recommendations stated:

"With respect to administrative leave for health care workers, the ACIP does not believe that health care workers need to be placed on leave because they received a smallpox vaccination. Administrative leave is not required routinely for newly vaccinated healthcare workers unless they are physically unable to work due to systemic signs and symptoms of illness, extensive skin lesions which cannot be adequately covered, or if they do not adhere to the recommended infection control precautions. It is important to realize that the very close contact required for transmission

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Ask Dr. Jeff or Dr. Brad your question!

Mail in your question or e-mail us at dr@stepproject.org

We will answer all questions and print those that space allows.

Ask Dr. Brad

by Dr Brad Lichtenstein

Q: *I am an HIV positive man on HAART who has been suffering with depression for several years. My doctor wants to prescribe antidepressants, but when I tried them in the past, I had side effects, insomnia and loss of sex drive. What might be some naturopathic alternatives?*

A: I suggest that you please read Depression and HIV in the Era of HAART by Dr. Elliott in this issue. Depression is multifactorial. The ideal goal of all healthcare practitioners is treat the underlying cause of the diagnosis or disease rather than chasing after and treating symptoms, whether with synthetic anti-depressants or with herbal medicines. While such treatments can be helpful in reducing the symptoms, it never addresses the underlying cause. For instance, if the theory is that the person is depressed due to a biochemical imbalance, the fundamental question remains – What is the cause of the biochemical disruption in the brain? Let me be clear, this does not suggest such treatments are without merit or necessity. Many people who have a history of chronic alcohol or recreational drug use (ecstasy, cocaine, crystal, marijuana) have an altered level of neurotransmitters level in their brain. Although there may be some alternative treatments that I will discuss, if this is the case, treatment with synthetic anti-depressants may be the only way to correct this imbalance, and hence give some relief from depression, which, if left untreated, could be more damaging to the health of the individual than HIV alone.

So what exactly causes changes in brain chemistry? The simple answer – everything! Depending upon the person to whom you are talking, the cause may be genetics, thought processes, nutrition, electromagnetic waves, sleep, breathing, etc. Copious studies, such as the numerous ones conducted at the University of Miami, continually show that cognitive reframing, the retraining your thought process in order to create new, more affirmative beliefs, has long-term, positive outcomes for health. Studies with HIV positive participants in group cognitive therapy reveal improvement in immune system parameters such as an increase in CD4 cells, NK cells and macrophages (all cells that fight infection), a decrease in serum cortisol levels (the stress related hormone which breaks down tissues), an increase in growth hormone (a hormone necessary for growth and rebuilding), and an increase in DHEA hormone (a precursor to all other sex hormones and connected with longevity). Biofeedback, which teaches you how to actively relax the body, is a form of reframing. Although it does not deal with the mental thought processes that lead to stress, it is a form of meditation in that it gives the mind something to focus on. When you are concentrating on one thing, lowering your heartbeat, for example, the mind is unable to fixate on negative, and hence depressing thoughts. Whenever you begin to imagine an unpleasant situation, and you feel your pulse or blood pressure rise, you are, in essence, creating a biochemical change in your body. Such a change will result in biochemical changes in the brain. Try this: imagine driving down the highway, thinking about a wonderful movie you had just seen. You are in the flow of traffic, which is jogging along at a fast clip. Suddenly, out of the corner of your eye, you spot a flashing red light. As you focus on it, you realize it is a police car. As you continue to notice it, you determine that it is in your lane, and that it is approaching you with increasing speed. Now it is right behind you. Before you continue to read further, what is happening to you? Most people who report reacting physically and emotionally to this visualization, describe sensations like sweaty palms, rapid pulse, shallow or held breath, and a feeling of butterflies in the stomach. However, they were not driving at the time they were visualizing this, such as you are not now. If such a thought, which is what visualization is, can trigger biochemical changes, what occurs throughout our daily lives when our minds wander all over the place? To finish, imagine that you pull over to the side of the road as the police car speed right past you and tickets the person in front of you. What is happening to you now? The point – if we can learn to

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of vaccinia to household contacts is unlikely to occur in the healthcare setting."

In the conclusion of their paper on CV, Neff and colleagues write:

"… any large-scale response, such as the one proposed by the CDC, has the potential to result in more cases of contact vaccinia. An orderly, systematic approach along with careful screening to identify possible vaccinia-susceptible individuals and household contacts and close monitoring for adverse effects are essential to reduce the risk of transmission of vaccinia following smallpox vaccination."

In several presentations that I have heard on the proposed smallpox vaccination programs, officials from both the National Institutes of Health and the CDC have expressed their concern and awareness of the risk of contact transmission of vaccinia to immunocompromised people. I think that a limited, planned smallpox vaccination program can be conducted which will minimize the risk of transmission of vaccinia or contact vaccinia. However, were there to be a small pox attack, and a massive vaccination program initiated, it is unclear if minimizing contact vaccinia could or would be a high priority. The CDC is currently recommending that the smallpox vaccine be given to a person with a weak immune system in the case of an actual face-face contact with a person infected with smallpox. The rationale for this recommendation is that the risk of death from smallpox would be greater than the risk of life-threatening complications from the vaccine.

For more in-depth materials about small pox vaccination see the CDC's web site at: http://www.bt.cdc.gov/agent/smallpox/vaccination/index.asp.

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focus our mind, our attention and our thoughts, we can influence our brain chemistry.

In studies of depression, one treatment actually stands alone in its effectiveness in elevating depressed mood. Exercise has been consistently shown to help patients deal with mild to severe depression. Although the mechanism is not known for certain, some hypothesize that moving the body, in any form, releases endorphins, chemical compounds similar to opiates, which elevate mood. Additionally, as you exercise, your breathing deepens. People suffering from depression have been shown to breathe either shallowly or hold their breath for prolonged periods of time. Such breathing patterns decreases the oxygen concentration while it increases the carbon dioxide concentration in the blood. Decreased oxygen to the brain can impair cognition, and hence, depress mood. Exercise also requires you to get up and not sit on the couch or bed, continually repeating negative thoughts about yourself. Like biofeedback, while exercising, you must massage your muscle of concentration, your brain, by focusing on what you are doing.

Nutritional deficiencies are also linked to biochemical imbalances. Both reverse transcriptase inhibitors and non-reverse transcriptase inhibitors deplete the body of several nutrients, such as copper, zinc, vitamin B12, and carnitine. Deficiencies in each of these are linked to depression. Copper deficiency, which is mild in the general population due to the deficiencies in the standard American diet, increases with medication use. When the body is deficient in copper, symptoms can range from anemia, hair loss, decreased body temperature, and depression. Since copper is required to generate and regulate hemoglobin, it is necessary to ensure that oxygen is transported efficiently throughout the body. Furthermore, copper is a fundamental component of two enzymes in the body. The first one is copper-zinc superoxide dismutase (SOD) which is a major anti-oxidant system in the body, while the second is dopamine beta-hydroxylase, which synthesizes norepinephrine, a major stress related hormone, and influences the neurotransmitters in the brain.

Zinc is required for growth and development of the cell in the body. It is a major factor in DNA and RNA synthesis, cell division, protein synthesis, and the expression of genes. In order for many of the enzyme systems in the body to function, zinc is necessary. Such systems include, but are not limited to, those that detoxify alcohol and drugs in the liver (alcohol dehydrogenase), excrete carbon dioxide (carbonic anhydrase), facilitate energy production in the mitochondria (cytochrome C), and breakdown proteins from food (carboxypeptidase). Regarding the immune system, zinc helps regulate CD4 cells, natural killer cells, and interleukin-2.

Like zinc, vitamin B-12 is also necessary for cell growth, maturation and development through its effect on DNA and RNA. B-12 is necessary for nerve function as well as the development of red blood cells. B-12 helps in the digestion of carbohydrates, fats and proteins. (for more detail about B-12, please read Mitochondrial Damage, STEP Perspective, Volume 2, Issue 2, 2002).

When these nutrients are reduced in the system, depression may occur. Such depression, which may be treated with synthetic anti-depressant agents, is linked to biochemistry. However, the mechanism is due to nutritional deficiencies, which, in turn, can affect serotonin, dompamine, and acetylcholine levels in the brain. Since each of these require a complex system of enzymes and cofactors in order to be synthesized, it is important not to overlook the other ingredients in the recipe. Some other nutritional deficiencies linked to depression are deficiencies in calcium, magnesium, folic acid, pyroxidine (B6), riboflavin, thiamine, and vitamin C. As mentioned in my article on Mitochondrial Damage, reverse transcriptase inhibi-

tors negatively affect certain enzymes that allow the mitochondria to replicate. Supplementations with some of the above listed nutrients may reduce such toxicity. Pleasantly, these nutrients, especially the B vitamins, can possibly provide relief in depression.

In addition to HAART medication, many of the prophylactic medications, such as Bactrim and Dapsone, also deplete the body of folic acid and almost all the other B vitamins. Furthermore, recreational drugs will rob the body of vital nutrients as well as have the potential to irreparably damage brain cells. Ecstasy oxidizes, or breaks down, dopamine in the brain. When this occurs, the oxidized dopamine can destroy nerve endings and neurotransmitters in the brain. For individuals already suffering from depression, this can exacerbate their condition, after they come down from their high.

Another nutrient in need of discussing is tryptophan. When the FDA had all forms of this essential amino acid removed from the counters of all health food stores across this country, it was done so out of fear and without much basis. One strain of tryptophan produced in Japan was contaminated. However, in their zeal and wielding the full scope of their political power, they banned all forms of tryptophan from being sold in the US. This amino acid is essential, meaning it cannot be produced in the body, and is required by the body in order to produce niacin (vitamin B3), proteins, and the neurotransmitter serotonin. People who are HIV positive have been shown to have lower levels of tryptophan, niacin, and serotonin in their blood. Deficiency in tryptophan can lead to symptoms that mirror vitamin B3, known as pellagra, such as dry skin, diarrhea, dementia, and possible death. Serotonin deficiency is considered one of cornerstones in the rationale for prescribing the class of drugs called selective serotonin re-uptake inhibitors. Levels of tryptophan can increase through supplementation of nicotinamide, a better tolerated form of niacin. Interestingly, studies suggest that supplementation with serotonin itself inhibits HIV from replicating in CD4 cells. Subjects taking AZT (zidovudine) had their serum and cerebrospinal fluid levels of tryptophan return to normal while on therapy. Not only would supplementation with tryptophan be beneficial for balancing moods, it may very well have a positive influence on HIV.

The issue of diet and lifestyle factors cannot be overlooked in dealing with depression. Repeated studies reveal the positive correlation between those who consume sugar and caffeine (in the form of coffee, cola and teas) and those who suffer from mild to moderate depression. Sugar does not include fresh, whole fruit, but does include fruit juice, honey, and molasses sweetened foods. Overconsumption of sugar and caffeine can put undo stress on the sympathetic nervous system, and can lead to hypoglycemia and potential hypothyroidism. Often the symptoms of both of these maladies are identical to symptoms of depression, and therefore these conditions needs to be explored further.

Essential fatty-acids, especially omega-3 fatty acids, tend to be low in patients with depression. Essential fatty acids, in the form of flax seed, borage and other plant oils, are important in regulating the lipid bi-layer of the cells of the body. Low fat diets have been shown to correlate to higher rates of suicide in people following such a dietary program. For people who are HIV positive with elevated triglycerides and cholesterol, essential fatty-acids are actually beneficial and can improve your mood.

So the take home message is this:

1. Take a good multi-vitamin and mineral supplement

2. Eat whole, fresh foods with lots of fruits and vegetables of different colors and rich in vegetable oils (no fried foods, please)

3. Avoid sugar, caffeine, alcohol, and recreational drugs

4. Exercise every day – do something that you enjoy, yoga, weight lifting, swimming, running and walking, just get out of the chair and move

5. Spend time each day practicing deep breathing, making sure you are not breathing abdominally alone

6. Journal – keep track of your negative thoughts you tell about yourself. Try to reframe them into a more positive outlook about yourself and your life. Imagine all your possibilities and potentials. Do not get trapped in the cycle of negative catastrophizing.

7. You are not alone - consult a qualified healthcare practitioner for assistance.

"TB" the #1 killer of people with HIV

TB is an infection caused by a bacterium called Mycobacteria Tuberculosis. It usually affects the lungs but can affect other organs also. TB is a very serious disease, it is estimated that one-third of the people in the world are infected with TB. 10 to 15 million Americans are infected carriers of TB. Tuberculosis "TB" is spread from person-to-person through the air. If someone with active TB coughs or sneezes on anyone who is close can breathe in the bacteria from the air and possibly become infected.

There are two stages of Tuberculosis. The first is "*Inactive TB infection*:" Meaning a person has been infected with the TB germ, but their body was able to fight the germ and keep them from getting sick. *People with inactive TB infection cannot spread the germ to others. *They will however test positive to a TB skin test. *They can take medications to kill the inactive germs in their body so the germs can't become active in the future. If you don't treat the inactive TB germ it can become active making you very sick and infectious later.

Then there is *"Active TB Disease:"* If a persons' immune system is weak or if they are a young child the TB germs can become active soon after infection. People with strong immune systems often won't get sick at all or not for many years. Symptoms of active TB disease are: *Cough that lasts longer than two weeks. *Cough that produces green or yellow sputum. *A fever that last more than three days. *Night sweats. *Unexplained weight loss of eight pounds or more. People with active TB must be isolated so they don't infect others. They need to take several medications but usually respond very quickly and feel better. They must take the medication for six months or more though; to make sure they don't relapse into sickness and become infectious again. They can also build resistance to the TB medications, if they don't take them correctly or for a long enough time.

The risk of developing active Tuberculosis is much higher in people that are infected with the HIV virus. Because HIV weakens the immune system, people that have both HIV and TB are 40 times more likely to develop active, infectious TB than people who are not HIV positive. One of the most important aspects of having HIV and TB is that they both make each other worse. TB makes the HIV virus multiply faster and HIV helps TB become active. It is very important for people that are HIV positive to be tested for TB. If infected you need to complete preventive therapy as soon as possible to prevent the TB germ from causing the active disease of Tuberculosis, causing your viral load to sky rocket , make you sick and possibly even kill you.

It is not easy to treat both TB and HIV at the same time. The drugs used to treat TB and HIV can both cause damage to the liver and kidneys. Also there can be negative drug interactions between the medications used to fight these two individual problems. It is not easy to handle the side effects of treating TB and it may take a long time but it can be cured. The treatment of TB in HIV positive people must be very carefully planned and monitored by a knowledgeable provider to insure that any problems that arise are picked-up and addressed quickly. Communication with your provider is important.

Erica Rocker, Treatment Educator BABES Network.

FDA Approves Zerit Once Daily, Extended Release Formulation

On December 31, 2002 the Food and Drug Administration approved a new, extended release formulation of ZERIT (stavudine , d4T) called ZERIT XR. This extended-release formulation has been shown to maintain viral suppression for 24 hours after once-daily dosing. The recommended dose of ZERIT XR is 100 mg once daily for individuals weighing at least 60 kg and 75 mg once daily for individuals weighing less than 60 kg. As with all antiretrovirals, it must be used in combination with at least two other anti-HIV drugs.

The following information was noted by the FDA in its approval announcement: In a clinical study conducted in 783 treatment-naive, HIV-infected individuals ZERIT XR was comparable to the previously approved twice daily formulation of ZERIT. In this randomized, controlled study, participants were randomized to either the extended release or standard formulation, in combination with Epivir and Sustiva. The proportion of people with HIV-RNA (viral load levels) below 400 copies at 48 weeks was 79% and 76% for the extended release and immediate release-containing regimens, respectively. For viral load under 50, the response rates were 55% and 57% for the new and old formulations, respectively. The tolerability and safety profile of the new once daily, extended release formulation is comparable to that of the previously approved twice-daily formulation.

This adds one more drug to the list of once-a-day FDA-approved antiretrovirals. The other drugs include Videx, Videx EC, Sustiva, Epivir, and Viread. It is expected that the new once-a-day protease, atazanavir, will be approved sometime in the next few months. For more information on once-a-day HIV treatments seen the article in the Fall 2002 STEP Perspective, *Once-Daily Antiretroviral Options*. (http://www.thebody.com/step/fall02/once_daily.html.)