

ACRIA Update
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Women and HIV Disease

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Women and HIV Disease

By Marshall J. Glesby MD PHD

Women currently constitute the fastest growing group of HIV positive persons in the United States and account for approximately 20% of AIDS cases nationwide and 40% worldwide. While the overall death rate from AIDS has declined dramatically in the U.S. in the past two years, the decrease has been substantially less in women than in men. Possible explanations for this discrepancy in death rates include delayed diagnosis of HIV in women, reduced access to medical care, and the fact that the epidemic in women began later than in men.

Aside from the differences in death rates, which may have more to do with social than biological factors, a number of differences may exist between men and women with regard to manifestations of HIV infection and its treatment. Certain opportunistic conditions, such as Kaposi's sarcoma, are much more common in men than women, while other problems, such as recurrent vaginal yeast infections and cervical cancer, are exclusive to women. Furthermore, HIV-related drug levels and drug toxicities may differ between the sexes due to differences in body weight, hormonal milieu, and metabolism.

The growing AIDS case rate in women has implications for children, since the overwhelming majority of HIV-positive children have acquired the virus from their mothers. Children living with HIV/AIDS are not simply smaller versions of their adult counterparts, and, like women, have unique considerations. Major differences between the course of HIV infection in children and adults relate to the child's developing immune system and lack of prior exposure to certain infectious agents.

Because of the growing importance of health issues pertaining to HIV positive women and children, we have devoted this expanded issue of ACRIA Update to this topic. A talented group of knowledgeable writers have contributed their expertise to this issue. Mary Jo Hoyt, Director of the Woman's HIV Program at St. Vincent's Hospital and Medical Center of New York City, has provided a thorough review of three important women's health problems and how HIV complicates them: cervical dysplasia, vaginal yeast infections, and menstrual abnormalities. Dr. Emily Erbeling, an expert on sexually transmitted diseases (STDs) at Johns Hopkins, has summarized the basics of STDs in women and how HIV and STDs interact with one another. Jill

Cadman, a member of ACRIA's Board of Directors, has comprehensively outlined the current state of knowledge of mother-to-child transmission of HIV.

AIDS Activist Tim Horn has provided an update on recent advances in pediatric HIV research. Last but not least, Marie St. Cyr has put a more human face on the HIV epidemic in women - particularly older women-based on her experiences as Executive Director of Iris House, a center for women living with HIV in New York City.

There are still many gaps in our knowledge of HIV in women and children. Our hope is that the next time we visit this subject further research will have provided us with more information to convey in an even larger publication.

Advances in Pediatric HIV Research

By Tim Horn

Despite the recent advancements in perinatal transmission research, the HIV/AIDS epidemic in children is hardly over. Even the most optimistic experts in the field acknowledge that, because women are among the fastest groups of people becoming infected with HIV, trends in perinatal transmission rates are likely to increase once again over time. It is estimated that more than 20,000 children in the United States are infected with HIV. While these children can expect to live longer, healthier lives in the age of highly active antiretroviral therapy (HAART), their treatment options are fewer and much less understood than those available for adults.

Over the past few years, there have been important advances in the diagnosis of HIV infection in children and infants. Until recently, it was difficult to confirm a potentially-exposed infant's HIV serostatus during the first year of his or her life; all children born to HIV-infected women carry their mother's HIV antibodies, sometimes for as long as 18 months after birth. In turn, standard ELISA and Western Blot testing are useless during this crucial time. Considering that nearly 25% of all HIV-infected infants rapidly progress to AIDS during the first year of life, pediatricians for many years had no choice but to aggressively monitor and treat all potentially-exposed infants during this time frame and to simply hope for the best. Now, due to the increasing availability of PCR technology and other virologic tests, it has become possible to confirm an HIV diagnosis in approximately 95% of all infants during the first month of life.

There has also been much progress made in understanding the natural course of HIV disease in children. HIV-infected children differ from HIV-infected adults in numerous ways. For starters, there is a much more rapid rate of disease progression in children; the average time to an AIDS diagnosis is 8 to 17 months in children, compared to 8 to 11 years in adults. Secondly, normal T-cell counts are significantly higher in children younger than 6 years of age and can fluctuate greatly. Thus, it is much harder to determine when opportunistic infections (OIs) might occur in HIV-infected children and to determine whether or not antiviral treatment or combinations of treatments are yielding the desired effect. Thirdly, HIV-infected children - possibly due to their high T-cell counts - have higher viral load levels than those typically seen in adults during the first several years of infection. Finally, HIV-infected children have an increased incidence of recurrent invasive bacterial infections. Moreover, OIs often represent primary disease with a more aggressive course, given lack of prior immunity. For example, an HIV positive child who has never been infected with the chicken pox virus may develop a severe case of chicken pox with initial (primary) infection. In contrast, many OIs in adults are reactivations of latent infections to which some level of immunity may exist. The chicken pox virus, which remains dormant inside of the body after the primary infection, may reactivate in an HIV positive adult or a child who has already had chicken pox, as shingles.

The number of treatments available to children has grown considerably over the last few years. The theory behind treating HIV-positive children is very similar to that of adults with HIV: HAART should be initiated promptly to slow HIV replication and disease progression. Yet, only a percentage of the total number of treatments approved for adults can be given to children, due to lack of pediatric safety data and formulation problems. Although some treatments are available in either a liquid or powder formulation for children, many other drugs are only available in adult-approved tablet or capsule formulas, which cannot be accurately broken down to meet pediatric dosing needs. While viral load has been shown to be an effective method of monitoring antiviral drug efficacy in pediatric patients, researchers have yet to determine exactly when children should start or switch antiretroviral therapy based on viral load results.

The antiviral treatments available in pediatric formulations include: AZT, ddI, d4T, 3TC, ritonavir, and nelfinavir. Glaxo-Wellcome's abacavir (1592) and Boehringer-Ingelheim's nevirapine are expected to be approved and available soon for children. Not surprisingly, many infants and children cannot tolerate many of these drugs (especially the protease inhibitors). Moreover, the majority of these treatments have only been tested in young children without prior antiretroviral experience. As a result, there is no way for antiretroviral-experienced children - who now account for the majority of children alive with HIV today - to know whether or not they will benefit from taking any of the other drugs approved or in development. As children get older, they also face dosing problems. For example, an eight or nine year-old child often requires a higher dose of a drug than recommended for infants, but still requires a dose less than that recommended for adults. This is especially true with the protease inhibitors, which require optimal dosing to delay resistance and prolong antiviral activity. Research looking at treatment options for antiretroviral-experienced children is still in its infancy. In turn, pediatricians do not yet have a solid standard-of-care to work from when treating older children with HIV.

Tim Horn is a member of the Pediatric AIDS Clinical Trial Group's Community Constituency Group.

Cervical Dysplasia and Cancer

By Mary Jo Hoytt, NP, MSN

Cervical dysplasia is the term used to describe abnormal cells on the cervix (the head and neck of the uterus). On a Pap smear report, dysplasia is referred to as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL). Cervical dysplasia is usually first discovered by Pap smear, where cells are swabbed from in and around the cervical os (opening of the cervix). Dysplastic changes on Pap smear are rated as "low grade" or "high grade"; high grade lesions are considered precursors to cervical cancer, while the significance of low grade dysplasia has not been established.

Cervical dysplasia and cervical cancer are strongly associated with, and believed to be caused by, specific subtypes of the sexually transmitted virus called HPV (human papillomavirus). Other subtypes of HPV cause genital and anal warts (condyloma acuminata) in men and women. HIV positive women have a high rate of persistent HPV infections, and a higher rate than HIV negative women with the types of HPV that are associated with the development of high grade dysplasia and cervical cancer. In one recent study, persistent HPV infections were found in 24 percent of HIV positive women but in only 4 percent of HIV negative women. Twenty percent of the HIV positive women and 3 percent of the HIV negative women had persistent infection with HPV 16 or HPV 18 viral types, which are most strongly associated with cervical cancer.

Numerous studies have also documented that HIV positive women are more likely than HIV negative women to have cervical dysplasia. A large study comparing HIV positive and HIV

negative women with documentation of dysplasia by colposcopy revealed 5 times as many HIV positive as HIV negative women with disease. Studies have observed, too, that the incidence of HPV-related dysplasia increases as immune function declines. Studies of HIV-positive women demonstrate that both rates of HPV infection and disease and of highgrade dysplasia increase as T cell counts decline.

The strong association between HPV infection and cervical dysplasia, the finding that HIV positive women are more likely to have persistent HPV infection of the specific subtypes associated with dysplasia, and that HIV positive women have a much higher incidence of dysplasia, all suggest that HIV-related immunosuppression either increases the risk of persistent HPV infection, or changes the natural history of HPV-related disease.

What, then, is the risk of developing invasive cervical cancer in women with HIV infection and HPV-related cervical dysplasia? The documentation of increased rates of cervical dysplasia prompted the CDC to add invasive cervical cancer to the AIDS surveillance case definition in 1993. However, much remains unknown about the incidence and natural history of this disease in HIV positive women.

Several small studies have found few, if any, cases of invasive cancer in HIV positive women with cervical dysplasia. In contrast, a study of women with invasive cervical cancer found that 19% of the cases in patients under the age of 50 were HIV positive. Other researchers have published case reports of rapidly progressive invasive cervical cancer in women with HIV. The bottom line is that the risk of invasive cervical cancer in HIV positive women with dysplasia may be increased, but the magnitude of the risk has not been adequately defined.

Colposcopy

Colposcopy is a method of examination of the cervix with a microscope that magnifies the cervical surface. Colposcopy is used to identify the site, severity, and extent of abnormal cell growth as well as to aid directed biopsy, plan treatment, and allow the use of conservative methods to treat early lesions. A speculum stays in place during the procedure, and is the same type which is used when you have a routine pelvic exam and Pap smear. The area to be colposcoped is wet with 5% acetic acid (a vinegar), which stains the HPV-affected tissues white, making them more clearly visible. Small samples of abnormal appearing tissue (a biopsy) may then be taken and sent to the lab for analysis. The procedure takes about 10 minutes, and can cause a pressure-type discomfort or menstrual-like cramping briefly. Scant bleeding is normal after the procedure.

Early Detection and Treatment

Although many questions remain about the risk of cervical cancer in HIV positive women, it is important to remember that cervical cancer is largely a preventable disease. Screening by Pap smear for all sexually active women can identify those with dysplastic precursor lesions so that they can be treated and monitored before more serious disease develops. With the high rates of HPV infection and dysplasia known to exist in the HIV-infected population, screening, early diagnosis, treatment and careful monitoring are crucial. With no medical intervention available to prevent HPV infection and disease, regular Pap smears, lower genital tract inspection, and appropriate colposcopic follow-up and treatment of abnormalities are the best hope for preventing serious disease in women with cervical dysplasia. Colposcopy is performed to evaluate atypical and dysplastic smears (see box to the upper left).

Unfortunately, at this point there is not a consensus of opinion regarding frequency of Pap smears or the management of abnormal findings in HIV positive women. Many clinicians who care for large numbers of HIV positive women and experts in HIV primary care for women have recommended more aggressive surveillance for genital tract dysplasia than the published

recommendations of the federal government's CDC or Agency for Health Care Policy and Research (AHCPR). These recommendations are based on the following facts:

1. Pap smears are about 80% sensitive in detecting abnormalities, meaning the Pap smear may miss 20% of abnormalities. Abnormalities are more common in HIV positive women, thus there is a greater risk that abnormalities will be missed. An undetected abnormality may progress to more serious disease more rapidly in an immunocompromised woman. Therefore, many clinicians feel the appropriate interval for Pap smear testing and genital tract inspection for HIV positive women with previously normal smears is every 6 months.

AHCPR guidelines: Annual Pap smears for women with normal results, and Pap smears every 6 months for women with a history of HPV or dysplasia. *CDC guidelines:* Two Pap smears in the first year after HIV diagnosis, then annually if negative. Pap smears every six months optional for high risk women.

2. Some women evaluated by colposcopy whose Pap smears showed only "atypia" have been found to have high-grade dysplasia. Therefore "atypical" smears, as well as all those revealing dysplasia, should be evaluated by colposcopy. Colposcopic evaluation of abnormal Pap smears should be performed within six to eight weeks of the abnormal Pap smear findings.

AHCPR guidelines: Refer all women with abnormal Pap results for colposcopy. *CDC guidelines:* Annual follow-up for atypical cells of undetermined significance.

3. Treatment failure and recurrence of dysplasia in HIV positive women is well documented. HIV positive women who have undergone any treatment for dysplasia in the past year should have a Pap smear three months after treatment and every three months after that for one year. After four negative Pap smears, they can resume a schedule of every six months.

There are a number of methods for destroying or removing dysplasia from the cervix (see box). However, dysplasia can recur after treatment, especially in HIV positive women. One study found that 62% of HIV positive women studied had recurrences of dysplasia three years after treatment. Recurrence was most common in women with advanced HIV disease, with 90% of those treated who had T-cells below 200 recurring by three years after treatment.

This is a discouraging finding for women who must deal with the realities of diagnosis, evaluation, and treatment of dysplasia in the face of concurrent HIV disease. In theory it is possible that highly active antiretroviral therapies will improve local and systemic immune function and treatment success in affected women, but this remains to be seen. In the meantime, HIV-infected women with dysplasia are left to deal with the difficult reality of frequent evaluation and possible frequent repetitions of uncomfortable procedures and treatments in an effort to avoid cervical cancer.

Treatment of Cervical Dysplasia

Treatment decisions are based on the grade of dysplasia (low vs. high), the location of the lesion on the cervix, the size of the lesion, whether the entire lesion is visible through the colposcope, and on previous treatment modalities employed.

Observation: It can be appropriate to leave low grade dysplastic lesions untreated if they are carefully and regularly evaluated by colposcopy and biopsy. When there are signs of higher grades of dysplasia, aggressive treatment should be offered.

Cryotherapy: Tissue destruction by freezing (application of a gas via a low temperature probe,

which freezes and destroys the area where it is applied). Done in the clinic or doctor's office. Mild discomfort, with slight spotting and watery vaginal discharge common after treatment.

Laser therapy: Tissue destruction by laser (a highly concentrated beam of light energy). Usually done in an outpatient surgical setting. Spotting and vaginal discharge after therapy common. Mildly uncomfortable.

Loop excision: Tissue removal by a "loop" of wire adjusted to be just larger than the size and shape of the affected zone of the cervix and the visible lesion. After the loop of tissue is removed, an endocervical curettage is done by scraping cells from inside the cervical canal (which removes tissue that may not be visible through the colposcope). Cramping is common during the procedure, and light bleeding is expected. Can be done in the clinic or office.

Cone biopsy: A "cone" of tissue is removed from in and around the cervical os, either by traditional surgery or by laser. Done in a surgical setting with some anesthesia. Light bleeding and discomfort common after the procedure.

Isotretinoin: Experimental. An oral drug, used to treat severe acne, which has shown some promise in treating HPV disease in immunocompetent women. Information on its effectiveness in HIV-infected women not yet available (Clinical trial: ACTG 293).

5-Fluorouracil: Experimental. A topical cream being studied for its effectiveness in preventing recurrence of disease in HIV positive women with high grade dysplasia that has been treated with standard therapy (ACTG 200).

Mary Jo Hoytt, NP, MSN is the director of the Women's Health Program, Section of HIV Medicine at St. Vincent's Hospital and Medical Center of New York City.

Vaginal Yeast Infections

By Mary Jo Hoytt

Vaginal candidiasis is a yeast infection usually caused by *Candida albicans*. *Candida* occurs normally in the mouth, digestive tract and vagina of a healthy person, but can overgrow and cause symptomatic infections, a common occurrence in persons with HIV infection. Candidiasis of the vagina occurs in women with or without HIV infection, but is more common in women with HIV infection. This yeast infection can occur in HIV positive women with relatively high T-cell counts, but the prevalence of vaginitis increases as T-cell counts decline, especially below 200. All women with frequent, recurrent, or persistent vaginal candidiasis should be tested for HIV infection.

Symptoms of vaginal candidiasis include a thick, white/yellow vaginal discharge (often described as "cottage cheese" in appearance) associated with mild to severe itching, burning discomfort, and pain with urination. Though many women "self-diagnose" yeast infections, and many providers diagnose the infection by its appearance, diagnosis can be confirmed by looking at a smear of the discharge under the microscope, or sending it to the lab to be grown in culture.

Yeast infections can usually be treated topically, with a cream or suppository that is inserted in the vagina before bed nightly for 3 to 7 nights. Several are available over the counter (without prescription), such as Monostat-7® or Gyne-Iotrimin®. If such treatments fail to relieve symptoms

and eradicate signs of infection, women should be checked for the possibility of a different infection. If no other infection exists, and yeast infection is confirmed, then oral azole agents (such as ketoconazole or fluconazole) may be required.

Frequent use of the azole agents for treatment in women with very low T-cell counts, however, can be problematic. Research has shown that these women are at risk for development of infection with resistant strains of *Candida*. These so called "resistant" infections will fail to respond to treatment with azole drugs, and may require treatment with topical or intravenous amphotericin B, a drug with multiple and sometimes severe side effects. For this reason, it is felt that it is best to use topical treatment for vaginal candidiasis first, and limit the use of azole drugs as much as possible to avoid development of resistant strains.

Use of fluconazole in low weekly doses for prophylaxis of candidiasis showed success in one study, without evidence of development of resistance. In a clinical trial CPCRA 010, which tested 200 mg of fluconazole per week as prophylaxis in 323 HIV positive women showed a 50% reduction in the incidence of thrush and vaginal yeast infections.

Menstrual Symptoms in HIV Positive Women

By Mary Jo Hoytt

Many women with HIV infection complain of an abnormal or changing menstrual cycle, and clinicians experienced in the care of women with HIV infection often feel that a higher than expected percentage of women in their care complain of menstrual problems. The absence of a menstrual period (amenorrhea) or lighter than normal menstrual bleeding (oligomenorrhea) from an HIV-related cause is speculative. In men however, gonadal (testicular) failure has been reported from early on in the epidemic, as have low testosterone levels, impotence, and testicular atrophy. Gonadal (ovarian) failure in women could present as a menstrual cycle disturbance. Heavy bleeding (menorrhagia) or painful periods (dysmenorrhea) could be explained by low platelets (thrombocytopenia) associated with HIV infection, or a complication of severe pelvic inflammatory disease, both conditions frequently associated with HIV disease.

Optimal care of HIV- infected women includes a good understanding of the clinical manifestations of gynecologic disease. However, in HIV-infected women, little is known about menstruation and abnormal vaginal bleeding, despite the importance of the menstrual history in evaluating ovarian function and detecting gynecologic disorders. Virtually nothing is known about any potential effects of newer antiretroviral therapies on hormonal levels and menstrual cycles of women.

Evaluation of HIV- related effects on the menstrual cycle is complicated by the fact that substance abuse, chronic disease, and significant weight loss can result in dysregulation of the hypothalamus (a part of the brain that regulates sex hormone secretion) and affect menstruation. Early on in the epidemic, a few cross-sectional studies described a high prevalence of oligomenorrhea and amenorrhea in women infected with HIV. However, where the data were compared with a control group, the disparity between substance abuse in the two groups was significant or not addressed at all. Because of a lack of comparable control groups, these studies did not really answer the question of whether HIV infection has an independent effect of increasing menstrual abnormalities.

In a later study, 55 HIV positive women and a matched control group underwent detailed gynecologic assessment, 71% of the infected women had asymptomatic HIV disease. In this study, there were no significant differences in the prevalence of menstrual abnormalities between the two groups. A larger study of the same design also suggested that neither HIV infection nor immunosuppression has a clinically relevant effect on menstruation or other vaginal bleeding. In

this study, most HIV-infected women menstruated about every 25-35 days, suggesting monthly ovulation (egg production) and an intact hormonal system.

HIV-infected women with abnormal or dramatically changed menstrual bleeding should have the full investigation accorded HIV-negative women to determine the cause of the abnormality. Heavy bleeding can cause anemia, a problem already prominent among women with advanced HIV infection, and can be a symptom of an underlying problem such as a fibroid tumor, blood clotting problems, or infection. Amenorrhea can be a symptom of pregnancy, ovarian cyst, ovarian failure, or menopause. Missing two periods (if pregnancy is ruled out) requires investigation by pelvic exam and blood tests to determine if the problem lies within the reproductive tract or not. In the course of identifying the cause of menstrual irregularities, women should report to their providers any change in drug therapy, use of recreational drugs, changes in weight, and all related symptoms.

HIV and Sexually Transmitted Diseases

By Emily Erbelding, MD, MPH

Issues of reproductive health, including sexually transmitted diseases (STDs), are among the most common reasons that women come to learn of their HIV positive diagnosis. This article will focus on treatable STDs encountered among women in the US and their relationship to HIV disease.

Non-ulcerative STDs

Gonorrhea and chlamydia are two common STDs which do not cause ulcers of the genitals. There were approximately 325,000 gonorrhea cases reported in the United States for 1996, and approximately 490,000 cases of chlamydia. Rates of gonorrhea in the U.S. are highest among minorities living in poverty, while chlamydia tends to be widely distributed among all racial and ethnic groups. The disease rate for chlamydia alone exceeds that of any other infection in the U.S. for which notification of public health agencies is required, and the reported rate of disease for women is more than five times that of men. The difference in reported rates for men and women is attributable to national screening strategies that are designed to focus on women. Screening strategies reflect the fact that the complications of chlamydia infection in women are severe (for example, infertility) and many infected women have no symptoms at all. Gonorrhea and chlamydia are similar in that they predominate in adolescents, they both infect the cervix, and they both cause a serious infection of the upper reproductive tract (uterine lining and fallopian tubes) known as pelvic inflammatory disease.

Infection of the vagina due to *Trichomonas* is reported to be the most common treatable STD in women by the World Health Organization. In the U.S., doctors are not required to notify public health authorities when a case is diagnosed, so that estimates of the extent of disease among women compared to that of other STDs are difficult to make. Trichomoniasis does not cause severe complications of the female reproductive tract as seen with gonorrhea or chlamydia; thus, trichomoniasis has been regarded as a nuisance condition of little consequence. However, it can cause severe itching and irritation in women, and it has been reported to be the most common STD in HIV-infected women in many clinic settings.

Genital Ulcer Disease (GUD)

In the U.S., genital ulcers are almost always caused by either herpes or by syphilis. Chancroid, another cause of GUD, causes occasional urban epidemics of genital ulcers in the southeastern U.S., but there were less than 400 cases reported to the CDC in 1996, making it much less significant than syphilis and genital herpes. Chancroid is more common in the developing world.

Genital herpes is classically caused by herpes simplex virus 2 (HSV-2), but also can be caused by the same virus that causes cold sores (HSV-1). Cases of genital herpes are not reported routinely to public health authorities. Because infection is lifelong and recurrent outbreaks are part of the disease, the rate of new infections in the U.S. is difficult to estimate. However, it is clear from population surveys that genital herpes has become much more frequent in the U.S. since the 1970s, with rates of infection rising dramatically among adolescents and young adults.

Unlike herpes, syphilis is a readily curable infection that public health authorities have targeted for extinction in the U.S. After a rise in U.S. syphilis rates in the late 1980's associated with the use of crack cocaine, the disease is now on the decline. As with gonorrhea, syphilis is often concentrated among minority men and women living in poverty, with rates among African-Americans 40 to 50-fold greater than among whites.

STDs and HIV Progression

Researchers have been concerned about the possibility that STDs might accelerate the progression of HIV disease. This concern is based on observations that activation of the body's immune system, either through infections or administering vaccines, may temporarily increase HIV viral load. While the clinical importance of such viral load increases is not definitively known, studies of HIV positive persons with tuberculosis (TB)-an infection that may cause increases in HIV viral load have demonstrated more rapid HIV disease progression. Could similar effects be caused by STDs? An increase in the amount of HIV in genital secretions has been noted with several different STDs, but it is not clear whether this increase in HIV replication is confined to the genital compartment or more wide spread in the body. Because some STDs, such as syphilis, cause widespread immune stimulation, an increase in plasma viral load (in the blood) would be predicted.

Impact of STDs on HIV Transmission

The possibility that STDs act as "cofactors" to facilitate HIV spread has been an important public health question in the past decade. HIV has spread through heterosexual contact in some parts of the developing world such as sub-Saharan Africa, where other STDs are very prevalent, at a startling rate. Studies have now conclusively shown that untreated STDs in a community enhance the spread of HIV. Improved STD services at the community level in rural Tanzanian villages resulted in a 38% lower rate of new HIV cases compared to villages where "usual care" for STDs was delivered. At the individual level, treatment of gonorrhea, chlamydia, and genital ulcers at a women's clinic in Abidjan (the Ivory Coast) resulted in lowering the amount of HIV in vaginal secretions. Thus, it is clear that untreated STDs make those who are HIV-infected more likely to pass HIV along to their sex partners. It is also clear that untreated STDs make those who are HIV negative more susceptible to acquiring HIV infection from an HIV positive partner. This "epidemiologic synergy" between HIV and other STDs makes early STD diagnosis and treatment a high priority wherever HIV poses a threat to the public health. In the U.S., meeting this priority will require better access to quality reproductive healthcare for both HIV positive and HIV negative women.

Treatment

Standard treatment regimens for most STDs are effective in those who also have HIV infection. Initial reports focusing on the interaction of HIV and syphilis indicated that those with HIV and syphilis might suffer complications of syphilis (neurosyphilis, syphilis of the brain, has been a particular concern) more frequently than those without HIV who acquire syphilis. However, a recent CDC study evaluating the response to treatment for early-stage syphilis among those who were HIV positive and HIV negative found that there was no major difference between groups. Most experts currently recommend a spinal tap to rule out evidence of central nervous system infection in HIV positive individuals who have a blood test positive for syphilis but who do not have clinical signs proving that their infection was recently acquired (either a genital ulcer or a characteristic syphilis rash).

Prevention

Because routes of transmission are similar for HIV and other STDs, similar prevention methods work to keep those who have HIV from acquiring another STD or from transmitting HIV to their partners, and prevent those who are HIV negative from acquiring HIV/STDs. Decreasing the frequency of partner change, seeking STD treatment early (as soon as any symptom appears), and using condoms consistently are behaviors under an individual's control that can minimize STD/HIV transmission risk. However, because some women may have little control over whether a male partner uses a condom, there is clearly an urgent need for better female-controlled prevention methods. Vaginal microbicides that are safe and acceptable are undergoing testing, mostly in developing countries, as a way to limit the heterosexual spread of HIV.

At the community level, STD/HIV prevention methods include adding HIV/STD education to the information taught in schools, improving the quality of STD/HIV counseling and treatment among primary care providers, and increasing access to reproductive health care among those who are uninsured. Expanded access to substance abuse treatment may have an indirect effect on STD prevention at the community level if expanded services decrease an important driving force for high risk sexual behavior.

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Older Women and HIV: A New Challenge

By Marie St. Cyr

We closed 1997 with hope for an improved life for all people living with HIV/AIDS. However, AIDS is now the 4th leading killer of women in New York City and at Iris House, where we serve women confronting this disease, this fact is particularly troubling.

We are encouraged by the reduction in death rates among people with AIDS, but concerned that the rate among women still lags that of men by 6 percent. Additionally, in our East Harlem Neighborhood, the rate of HIV cases per 100,000 people has increased steadily from 1,171 in 1991, to 3,404 in 1996, and 3,956 in 1997.

At Iris House, a new face of the epidemic has begun to disturb us. It is that of grandmothers, women between 45 and 62, who are increasingly being diagnosed with HIV/AIDS. As usual, we are playing catch up. The prevention efforts of the City of New York focus on a population targeted according to past AIDS incidence, mainly gay men, IV drug users and their partners, as a result, we may very well have missed the sexually active heterosexual men and women over 50 who may feel that they are not threatened by HIV.

One recent case we faced is particularly startling. A 58 year-old grandmother and main family caregiver came to us in search of information to help her newly HIV diagnosed son. A young married man, he and his wife were expecting the birth of a new child. In the event that the mother was also infected, the family's hope for a HIV negative grandchild was heightened by the new treatment protocols which could reduce the risks to the baby. A few months after coming to us, the grandmother not only discovered that she was HIV positive, but that her similarly aged sister had just been diagnosed HIV positive as well!

AIDS incidence among older women is a new nightmare for HIV care. Many of these women already battle other chronic illnesses such as diabetes, hypertension, obesity and the host of social and financial ills facing women on fixed incomes. Many of them have no idea of their risk

until diagnosis. These grandmothers often assume the role of mother to their grandchildren who have often times already lost their parents to AIDS. As the longstanding pillars of support for our communities, we cannot afford to also lose them to this epidemic.

So 1998 presents new challenges: ensuring that all women have access to the ever changing number of AIDS treatments, supporting them to maintain their adherence, assisting them with unexpected side effects and challenging their hopes. Our response to these challenges must maintain women's integrity and the dignity they deserve.

Marie St. Cyr is the Executive director of Iris House, a residence and service provider for women living with HIV in Harlem.

Strategies for Interrupting Mother-to-Child Transmission

By Jill Cadman

As new AIDS treatments are prolonging lives, many HIV-infected individuals are feeling optimistic for the first time and thinking about their futures. For some this means starting a family, a hope they may have abandoned since the news of their diagnosis. Fortunately, just as there have been advances in the treatment of HIV-infected adults, there have also been advances in the prevention of mother-to-child transmission (vertical transmission). However, choices for pregnant HIV positive women are complex and it is not always clear what is best for mother and baby.

Factors Associated with Vertical

Transmission The condition of the mother's immune system has been shown by several researchers to be related to the rate of vertical transmission. According to Yvonne Bryson, MD, of UCLA, "women with advanced clinical disease and most probably primary infection during pregnancy have a high risk of transmission."

There is some controversy over the role of HIV viral load in vertical transmission. It is thought that viral load is certainly related to transmission but that it is not the only factor. Women who transmit HIV infection to their infants have a wide variation of viral loads. However, women with lower viral loads tend to have lower risk and those transmissions that do take place at lower levels may occur at delivery. In a recently reported study from London, the mother's viral load was found to be a better predictor of vertical transmission than T-cell counts. The estimated rates of transmission were 2 percent for women with 1,000 HIV RNA copies/ml, 11 percent for 10,000 copies/ml and 40 percent at 100,000 copies/ml. Ultimately, however, viral load may be more useful in determining the mother's own treatment than in predicting if she will transmit the virus to her baby. The healthier the woman, the better the chance that she will not transmit. For all of the above reasons, lowering the mother's viral load is desirable.

Certain obstetrical factors may increase the risk of transmission by causing trauma to the baby. These include some tests, instruments and procedures used during pregnancy and delivery. Amniocentesis, internal fetal and labor monitoring during delivery, episiotomy (an incision near the vagina to widen the opening for the baby to come through), urinary catheters, and forceps and vacuum extractors should be utilized only if medically necessary for the safety of the mother and fetus. Artificial rupturing of membranes (breaking of the "bag of waters") should also be avoided where possible. According to several studies, the risk of vertical transmission increases when the membranes rupture more than four hours before delivery.

It has been suggested that Cesarean section could reduce the risk of vertical transmission. Numerous studies have examined this question and have come up with conflicting findings. The pooled results of eleven studies found that there was a higher risk of transmission for infants

delivered vaginally than infants delivered by C-section. However it is difficult to control for factors such as obstetrical emergencies, degree of illness of the mother, and type and amount of prenatal care. One study that was able to control for time of ruptured membranes found no difference in transmission rate between C-sections and vaginal deliveries.

The increased risk of surgery for an immunocompromised woman must be balanced against the statistical difference in risk of transmission. A study in Italy found that HIV positive mothers are at an increased risk for post-operative complications when delivered by C-section . Many obstetricians prefer antiretroviral drug treatment to C-sections, since AZT has been proven effective in reducing transmission regardless of mode of delivery.

Time of Transmission

Although the exact mechanism of transmission is still unclear, it is known that babies can be infected during pregnancy (in utero), at time of delivery (intrapartum) after delivery, usually by breast-feeding (or postpartum). HIV can infect the infant as early as eight weeks. There appears to be an increased rate of spontaneous abortions (miscarriage) when transmission occurs in the first trimester. Transmission occurring later in pregnancy is more responsive to interventions. The mother can be treated with antiretrovirals that pass through the placenta to the fetus.

Lynne Mofenson, MD, of the National Institutes of Health, feels that the majority of transmissions appear to occur during labor and delivery. Interventions that provide treatment directly to the baby are necessary for preventing transmission at that time. According to Dr. Bryson, evidence in support of intrapartum transmission includes the significant proportion of infants (50% -70%) who are HIV culture-negative at birth and positive at a later date. The other 30% to 50% of positive newborns can be diagnosed positive by culture at birth. This suggests that babies who are negative by culture at birth but eventually test positive are being infected at the time of delivery. Treatments given to newborns who initially test negative may still be worthwhile as post-exposure prophylaxis or early therapy.

ACTG 076: A Watershed Clinical Trial

ACTG 076 was a study to determine if the rate of vertical transmission could be reduced. At the time ACTG 076 was proposed, it was unknown whether AZT would have any impact. In fact, the trial was very controversial as many activists felt AZT might not help the mother or the fetus and might, in fact, do damage. Despite these concerns, the trial was undertaken and the results were impressive enough to change the standard of care for pregnant HIV positive women.

The design of the 076 protocol (see Table 1) demonstrated the uncertainty of the investigators as to when vertical transmission actually took place and at what point an intervention would be most effective. The rationale for the protocol was to interrupt transmission at each of the three possible stages when it might occur. Oral AZT was administered during pregnancy to target transmission that occurred in utero. Treatment began after the first trimester, which is the period during gestation of maximum organ development, to avoid a potentially higher risk of birth defects. AZT infusions were given during delivery so that the drug could cross the placenta and rapidly produce AZT levels in the baby. This was important during the period of intense HIV exposure through infected blood and secretions when the baby was passing through the birth canal. Oral AZT syrup was then administered to the newborn because of the possibility of infected maternal blood having passed into the fetal blood stream during labor and delivery. In this way the AZT possibly switches from pre-exposure prophylaxis to post-exposure prophylaxis for the baby.

Table 1	ACTG 076 Protocol
Period of Drug Administration	Drug Dosage and Interval

Before birth (ante partum)	100 mg AZT given orally five times daily, beginning at 14-34 weeks gestation and continued throughout pregnancy
During labor (intra partum)	Continuous IV infusion of AZT until delivery
Newborn (post partum)	AZT syrup orally administered to the newborn according to body weight every six hours through the first six weeks

This was important during the period of intense HIV exposure through infected blood and secretions when the baby was passing through the birth canal. Oral AZT syrup was then administered to the newborn because of the possibility of infected maternal blood having passed into the fetal blood stream during labor and delivery. In this way the AZT possibly switches from pre-exposure prophylaxis to post-exposure prophylaxis for the baby.

The results of ACTG 076 demonstrated a 67% reduction in the risk of vertical transmission in the AZT treated group at all levels of maternal viral load. Yet it is still unclear exactly how AZT reduced transmission, or indeed which component of the regimen worked. Since AZT only modestly reduced maternal viral load, decrease in HIV RNA by AZT did not account for its effect in 076, raising the possibility that effectiveness may, in part, be due to the presence of the drug in the infant during labor. Global studies of short course AZT treatment to determine which part of the protocol was most important recently demonstrated that AZT given in the last four weeks of pregnancy, then orally to the woman during labor but not given to the newborn, reduced transmission by 51%. This finding seems to support the theory that interventions around the time of late gestation and delivery are most efficacious. For the time being, the recommendation for women in the U.S. to use the more effective longer 076 protocol will not change.

ACTG 185: Extending 076 Results to a Sicker Population

ACTG 185 was a study on vertical transmission that added an additional treatment component to the 076 protocol. ACTG 185 looked at combination therapy with HIVIG (an immunoglobulin preparation containing high levels of antibodies to HIV) versus IVIG (a standard immunoglobulin preparation that does not contain HIV antibodies) in addition to the 076 regimen. All participants had more advanced disease than the 076 cohort and required antiretroviral therapy for their own health (see Table 2).

Table 2 Comparison of ACTG 185 and ACTG 076 Participants

	ACTG 076	ACTG 185
Entry CD4 Count	Greater than (>) 200	Less than (<) 500
Median	550	306
% CD4 <200	0%	23%
AZT Prior to Pregnancy	5% (duration: a few weeks)	21% (duration: weeks to months)
Median Entry Viral Load	5,700 (PCR)	18,500 (NASBA)
%Viral Load >50,000	7%	27%

Researchers expected the transmission rate to be higher in such a less healthy group. However, the trial was halted in March 1997 when the transmission rate was found to be the same in both treatment arms, 4.8%, which made comparison impossible. This unexpectedly low rate was less than the 8% rate found in the 076 study. In the 185 study, the participants received AZT earlier in pregnancy by about 2 months, for 19.3 weeks as opposed to 11 weeks in 076.

Transmission was associated with viral load levels measured at the time of entry into the study and at delivery of the baby, with each one log (10-fold) increment of HIV RNA linked with a 3-4 fold increase in risk of vertical transmission. None of the women with HIV RNA below 500 copies/ml at delivery transmitted, while 5% of those with levels over 500 copies/ml transmitted. Based on these results, Dr. Mofenson suggested that for pregnant women receiving AZT treatment, decreasing viral load to low levels may further reduce transmission.

Concerns About AZT

AZT is a category C drug (see Table 3). Concerns regarding its use during pregnancy include the potential risk for the future development of cancer in children born to women taking the drug. This risk could theoretically extend past childhood into adulthood. Two animal studies have looked at the risk of cancer in offspring exposed to AZT. A National Cancer Institute (NCI) study showed an increased rate of tumors in offspring of mice given very large quantities of AZT, just below the maximum tolerable dose. A GlaxoWellcome study demonstrated no increase in tumors in offspring of mice receiving doses whose range was more in line with the human dose, 1/12th to 1/50th of the NCI dose. A National Institute of Health (NIH) panel convened to evaluate the studies voted unanimously that the benefits of AZT use outweigh the risks. The panel also concluded that information regarding the carcinogenic risk should be discussed with all HIVpositive pregnant women during treatment counseling.

Celine Hanson, M.D., of Baylor College of Medicine in Texas, presented information at the National Conference on Women and HIV on the lack of tumors in 734 infants. Dr. Hanson analyzed infants with fetal or neonatal exposure to AZT. No tumors of any nature were reported in any of the children, who have been followed for an average of one to three years, with the longest time being six years. Since the follow up period was relatively short, it is possible that tumors could appear in AZT exposed children during adolescence or adulthood, regardless of the child's HIV status.

Neurodevelopment tests have determined no difference in infants exposed to AZT versus placebo. Growth, including weight, height, and head circumference, have also shown no difference between the groups. In addition, no increase in congenital abnormalities compared to the general population was seen in ACTG 076 or the Antiretroviral Pregnancy Registry. *The Antiretroviral Pregnancy Registry has been established to collect observational data on antiretroviral exposure during pregnancy in order to assess the potential for birth defects. Registry data is used to supplement studies and is provided to clinicians to assist patients in making informed treatment decisions. Health care providers can request information and report data on patients by calling 800-722-9292, extension 38465.*

Table 3 **FDA Pregnancy Classification of Antiretroviral Drugs**

Drug	Pregnancy Category
AZT (Retrovir™)	C
ddC (Hivid™)	C
ddl (Videx™)	B
delavirdine (Rescriptor™)	B
d4T (Zerit™)	C

indinavir (Crixivan™)	C
nelfinavir (Viracept™)	B
nevirapine (Viramune™)	C
ritonavir (Norvir™)	B
saquinavir (Invirase™, Fortavase™)	B
3TC (Eprivir™)	C

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters). **B:** Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of women have not been conducted. **C:** Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.* **D:** Positive evidence of human fetal risk based on adverse reaction data from research studies or market experiences (after the drug has been approved), but the potential benefits from the use of this drug in pregnant women may be acceptable despite its potential risks. **X:** Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

**Some category C drugs that are carcinogenic in animals, such as acyclovir which has been available for many years, have been shown over time to be relatively safe in human pregnancy and not to cause tumors.*

The Public Health Service (PHS)

Pregnancy Guidelines

The federal government has released a series of documents that attempt to provide principles and guidelines for the use of antiretroviral therapies. The underlying premise is that HIV infection should almost always be treated with a combination of at least three drugs that include a protease inhibitor and two nucleoside analogs. Principle #8 states, "women should receive optimal antiretroviral therapy regardless of pregnancy status," further explaining that, "in general, pregnancy should not compromise optimal HIV therapy for the mother." By optimal therapy the panel means the timely use of combination therapy.

Clinical scenarios are presented in the pregnancy guidelines to address specific situations and offer recommendations for the use of antiretroviral drugs to reduce vertical transmission. For treatment-naïve women in the first trimester of pregnancy, it is recommended, if clinically possible, to delay therapy until after 10 to 12 weeks gestation. This recommendation is based on the fact that there is no scientific information regarding the safety of any antiretroviral during this period. After the first trimester, such women should be offered the three-part ACTG 076 regimen plus other antiretroviral drugs as needed for their own health.

Women who are already on antiretroviral drugs when they become pregnant have to consider whether or not to continue therapy during their first trimester. If a woman decides to stop therapy as a precaution against possibly impairing early development of the fetus, all drugs should be discontinued together, and reintroduced simultaneously to minimize the development of resistance. However, if a woman learns of a pregnancy after the first trimester has ended, it is recommended that she continue antiretroviral therapy. If the current regimen does not include AZT, the addition or substitution of AZT is recommended regardless of the antiretroviral regimen used during pregnancy.

Stopping treatment is a hard choice and may depend on the woman's disease stage. If she is on highly active antiretroviral therapy (HAART) because of a high viral load, then terminating one or all of her medications risks an increase in viral load or the development of drug resistance which

might increase the possibility of vertical transmission. Each woman must weigh the danger to fetal development versus the risk of fetal infection. Due to the lack of research on the safety and efficacy of antiretroviral use during pregnancy, this is a difficult decision.

The thrust of these recommendations is that overall, treatment should continue during pregnancy after the first trimester, but the specifics of the treatment do not go beyond the three-part AZT protocol. Clearly AZT monotherapy is substandard therapy for HIV infection. The goals of treatment for an HIV positive pregnant woman are two-fold: one is the use of drugs for improvement or maintenance of maternal health, and the second is the interruption of vertical transmission. Ideally these two intentions do not conflict. While AZT monotherapy is the only proven means of reducing the risk of transmission, combination therapy may be better for the mother's own treatment. Women need to know how other antiretroviral drugs will affect the fetus at each stage of development. This information is not currently available.

AZT Resistance, Other Antiretroviral Combinations and Current Clinical Trials

Many people have expressed concern over the possible development of drug resistance in women who receive AZT monotherapy during pregnancy. Resistance can develop in some individuals in as little as six months on AZT monotherapy. According to the federal PHS treatment guidelines for HIV-infected (non-pregnant) adults, asymptomatic individuals with CD4 cell counts above 500 and low viral load would have the option of delaying treatment. However, pregnant women in this category will be offered AZT monotherapy to begin as early as 14 weeks and continue for an additional five to six months until the birth of the child. Development of AZT resistance during this period would have permanent ramifications on future treatment choices for the mother and resistant maternal virus might not protect the fetus.

In a study presented in January 1997 by Dr. Scott Eastman at the Fourth Conference on Retroviruses and Opportunistic Infections, participants from ACTG 076 were evaluated to determine the prevalence of AZT resistance at entry and delivery. Both the baseline prevalence and the development of resistance were not found to be overwhelming. ACTG 185 demonstrated that the duration of AZT use in women with more advanced disease, many of whom received prolonged AZT prior to pregnancy, was not associated with increased risk of transmission. However, two other studies indicated the opposite. French and American studies found higher rates of transmission in women who had used AZT prior to pregnancy. It is still not clear whether AZT-resistant virus and prior AZT use specifically increases the likelihood of vertical transmission, although according to Dr. Mofenson, it seems intuitively possible. It also remains to be seen what would happen if a woman with AZT-resistant virus used another antiretroviral agent or agents during pregnancy.

Clearly more information is needed to understand the safety and efficacy of the other anti-HIV drugs in preventing vertical transmission. This becomes increasingly important as more HIV positive women are treated with antiretroviral agents prior to pregnancy. Such women may, in fact, already be AZT-resistant at the time they become pregnant and need to be treated with combination therapy during pregnancy. Trials are underway looking at the other drugs, including the protease inhibitors (see Table 4), but it will be a long while before there will be conclusive answers. However, as ACTG 076 so powerfully demonstrated, the rate of vertical transmission can be dramatically reduced using antiretroviral drugs. Already, with the wide implementation of this protocol in clinical practice, the rate of vertical transmission nationally and in other industrialized nations has been brought down significantly, to 3%-5%. Hopefully, the combination of even more potent combinations can bring down the rate of vertical transmission even further.

**Table
4**

**Ongoing Clinical Trials to Prevent Mother-Child
Transmission**

Protocol

Study Design

Number	
ACTG 316	(nevirapine or placebo) + standard of care
ACTG 353	nelfinavir/3TC/AZT
ACTG 354	ritonavir/3TC/AZT
ACTG 357	abacavir/3TC/AZT
ACTG 358	indinavir/3TC/AZT
ACTG 324	Abbreviated 076 regimen

Jill Cadman has been with Gay Men's Health Crisis as a volunteer and staff member for the past five years. She is currently the Associate Editor for Treatment Issues, the GMHC AIDS treatment newsletter. Jill is also on ACRIA's Board of Directors.

ACRIA NEWS

Twice a Day Crixivan™ Study

Both common sense and research studies dictate that the fewer times that pills have to be taken per day, the more likely people are to take them consistently. With this in mind, several manufacturers of protease inhibitors which are usually taken three times a day have begun to study their use twice a day. Preliminary data from studies conducted by Merck and Agouron in persons who are protease inhibitor naïve suggest that it may be possible to take Crixivan™ (indinavir) and Viracept™ (nelfinavir) twice a day. The duration of follow-up of these relatively small studies is limited to date, so it is not known definitively whether the twice a day dosing is as safe and effective as the three times a day dosing. None of the studies reported thus far have taken people who are already on the usual dose and switched them to twice a day dosing.

CRIA is participating in a multicenter study sponsored by Merck which is designed to address the question of whether persons taking the usual dose of Crixivan™ can safely be changed to twice a day dosing (see page 2). In this study, eligible persons who have been taking Crixivan» plus two nucleoside analog drugs for at least six months and have viral loads less than 400 will be randomly assigned to continue the usual dose of 800 mg every 8 hours or to switch to 1200 mg every 12 hours. For more information, call Dr. Douglas Mendez at 212-924-3934.

New Community Advisory Board

CRIA is in the process of establishing a volunteer Community Advisory Board (CAB) to provide oversight of our Treatment Education Program. The CAB will review and evaluate all service components of this critical program on a regular basis. Its purpose will be to ensure that treatment education is provided in a culturally and linguistically appropriate format to a broad and fully inclusive cross section of people living with AIDS in New York City.

CRIA is accepting nominations for the CAB membership. If you know a PLWA who is interested in volunteering to serve on our CAB , please fax or mail a letter of recommendation to CRIA. No phone calls please.

CRIA's Women's Treatment Education Services

CRIA is proud to announce an initiative to provide specialized treatment education sessions to underserved women living with HIV/AIDS in New York City. This initiative has been made possible by the generous support of the Liz Claiborne Foundation. Contact CRIA's Treatment Education Department at 212- 924-3934 for information on how to access this service.

TRIALS NOW ENROLLING

Adefovir Dipivoxil for Antiretroviral Naive Patients

CRIA is participating in a 48 week study of Gilead Sciences' nucleotide analog drug adefovir dipivoxil (Preveon™). Adefovir is a new type of drug that is active against HIV as well as some other viruses such as CMV, hepatitis B virus, and herpes viruses. The study is of HIV+ persons with more than 100 T-cells and HIV viral load of greater than 5,000 who have not taken other anti-HIV drugs in the past. Participants will be assigned to one of three treatments, all of which include the protease inhibitor indinavir (Crixivan™). Participants will be reimbursed \$15 per scheduled visit after enrollment.

Adefovir Dipivoxil for Protease Inhibitor Naive Patients

CRIA is also participating in a 48 week study of adefovir dipivoxil for HIV+ persons who have taken nucleoside analog drugs (e.g., AZT, 3TC, ddI, d4T, ddC) for at least four weeks. Participants will be switched to one of three possible combinations, all of which include adefovir dipivoxil and one or two protease inhibitors. To be eligible, participants must have more than 100 T-cells and a viral load greater than 5,000. Participants will be reimbursed \$15 per scheduled visit after enrollment.

Combination Study for Antiretroviral Naive Patients

CRIA is participating in a study comparing the three drug combination of Combivir™ (AZT/3TC) plus nelfinavir with the four drug combination of Combivir™ plus 1592U89 and the 141W94 protease inhibitor. To be eligible for the study participants must have a T-cell count of 50 or greater and a viral load of 5,000 or greater. The only prior treatment allowed is up to one week of 3TC or a protease inhibitor and up to four weeks with other nucleoside analog drugs. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

Twice a Day Crixivan™ Study

In this 24 week study, persons already taking Crixivan™ (indinavir) three times a day will be randomly assigned to continue this dose or change to 1200mg twice a day. To be eligible, you must be taking Crixivan™ plus two nucleoside drugs for the past 6 months, have undetectable viral load (less than 400 copies/ml), and have more than 100 T-cells. You must not have taken any other protease inhibitor. Participants will be reimbursed \$15 per scheduled visit after enrollment.

DMP 266 (Sustiva™) Study

DMP 266 is DuPont Merck's new non-nucleoside reverse transcriptase inhibitor (NNRTI) that appears to be quite active against HIV in early clinical studies when used in combination with other drugs. CRIA is participating in a study of DMP 266 for people with more than 50 T-cells and HIV viral loads greater than 10,000 who have not taken a protease inhibitor drug, 3TC, nevirapine, or delavirdine. Participants will be assigned to one of three combinations: AZT + 3TC + indinavir (Crixivan™), AZT + 3TC + DMP 266, or indinavir + DMP 266. The study will last 60 weeks and participants will be reimbursed \$15 per scheduled study visit after enrollment.

Oxandrolone for Women with Weight Loss

Oxandrolone is BTG's anabolic steroid hormone which has shown promise as a treatment for AIDS-related wasting in small, preliminary studies and, unlike testosterone, can be taken as a pill. CRIA is participating in a multicenter study of oxandrolone for AIDS-related wasting in women. In this study, different doses of oxandrolone will be compared with inactive pills (placebo) for 12 weeks, followed by a 24 week period during which all participants will receive oxandrolone. Participants must be HIV+ with unintentional weight loss of 10-20% of their usual body weight. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

Protease Inhibitor and Blood Sugar Study

CRIA is conducting a study to examine the effects of protease inhibitor use on responses to the oral glucose tolerance test (measurement of blood sugar levels after taking a drink with a high sugar content). To be eligible, participants must be about to start treatment with a protease inhibitor drug for the first time. Participants will be reimbursed \$30 for each of the first two visits and \$50 for the final visit.

SMART/EST Women's Project

CRIA is participating in a multicenter study to test a 10 week stress management program to teach women how to cope more effectively with their illness and everyday problems. Two approaches -individual and group relaxation training- are being compared. Women 18 years of age and older with a diagnosis of AIDS may be eligible. Participants will be reimbursed \$25 per visit after enrollment (up to \$575). Free child care and refreshments will be provided. For more information, call Debra Munger at 212- 924-3934.

Testosterone and MET-Rx™

CRIA is sponsoring a study of testosterone and MET-Rx™, a high protein nutritional supplement for treatment of AIDS-related wasting. Participants will receive testosterone or placebo injections in combination with MET-Rx or standard nutritional supplement. Participants must be HIV+ men with T-cell counts of less than 400, low testosterone levels, and weight loss or loss of lean body mass. For information, call Dr. Judith Rabkin 212-543-5762.

For an updated listing of our trials, please call 212-924-3934.

GENEROUS CONTRIBUTIONS

The following persons, corporations and organizations made major donations between December 16, 1997 and March 15, 1998 to support CRIA's search for effective AIDS treatments:

Agouron Pharmaceuticals, Inc.
Joe Andoe
Donald Baechler
John Baldessari
Sandra Bernhard
Bristol-Myers Squibb
Broadway Cares/Equity Fights AIDS
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The Isidore Stern Foundation
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Dorothy Heyman
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Michael Paller
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Bob Weinstein

ACRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. ACRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of ACRIA Update are available free to agencies that provide services to people living with HIV/AIDS. For more information, call Jonathan Deardoff at 212-924-3934 ext. 121.

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