

ACRIA Update

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Women and HIV Disease

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Women continue to represent the fastest growing group of HIV positive persons in the United States. It is estimated that women account for approximately 17% of AIDS cases nationwide and 40% worldwide. There are still many gaps in our knowledge of HIV in women. But, thankfully exciting new research is being conducted which should shed light on the many complicated issues that women with HIV face. We have devoted this issue of CRIA Update to discuss healthcare issues important to women with HIV/AIDS and have gathered a talented group of writers to address these important issues.

First, Anne Monroe, research associate at Cornell's HIV Clinical Trials Unit in New York City, has provided us with a medical update focusing on vaginitis and HPV from the 1999 Conference on Women and HIV/AIDS held in Los Angeles and an article focusing on women in clinical research. Next, Jill Cadman, a member of CRIA's Board of Directors and research associate at Bentley - Salick Medical Practice, has provided a comprehensive update of mother-to-child transmission of HIV. Followed by an article on pediatric treatment issues by regular contributor Tim Horn. Next Anne Forbes, Field Organizer for the Global Campaign for Microbicides and Women-Controlled STI/HIV Prevention Alternatives, and Polly Harrison, Ph.D., Director of the Alliance for Microbicide Development in Maryland, have comprehensively outlined the current state of knowledge of microbicides.

Last but not least, Kathryn Anastos, MD, Principal Investigator for the Women Interagency HIV Study (WIHS), NYC/Bronx consortium and Vice President and Chair, Ambulatory Services and Primary Care, Catholic Medical Centers of Brooklyn and Queens, has provided an update on HIV treatment recommendations for women.

We hope that the information in this issue will help women better understand some of the issues that are important to their health and well being.

J Daniel Stricker, Editor-in-Chief

Medical Update from the 1999 Conference on Women and HIV/AIDS

by Anne Monroe

The 1999 Conference on Women and HIV/AIDS brought 2000 participants, including 800 HIV-positive women, to Los Angeles to discuss clinical, prevention, and policy issues related to infected and affected women. The conference provided attendees with comprehensive information about HIV infection in women, a crucial tool for self-advocacy in HIV care.

Dr. Jean Anderson of the Women's Health Center in Baltimore, MD, presented a State of the Science lecture describing two common gynecologic conditions, vaginitis and HPV infection. Both of these conditions negatively impact quality of life for women living with HIV, and have implications for overall health and quality of life.

Vaginitis

Symptoms of vaginitis, the inflammation of the mucous membranes of the vagina, include pain, itching, and foul-smelling vaginal discharge. Infection with yeast or candida, a yeast-like fungus, trichomonas (protozoa), or gardnerella vaginalis (bacteria), can cause vaginitis.

Bacterial Vaginosis

It is estimated that 24-37% of all women seen at STD clinics have bacterial vaginosis, (vaginitis of a bacterial origin.) The condition is exhibited in 31-42% of HIV-infected women, with no significant difference in occurrence associated for different CD4 cell counts. Bacterial vaginosis occurs when the normal bacteria in the vagina, the lactobactillus dominant, are displaced by mixed strains of bacteria, including gardnerella vaginalis. There is increased risk of bacterial vaginosis associated with douching, sex with multiple partners, and inconsistent condom use. Complications associated with vaginosis include preterm delivery, low birthweight, postpartum endometritis (inflammation of the lining of the uterus), pelvic inflammatory disease and postabortal infection.

Several studies have shown an increased rate of sexual transmission of HIV related to bacterial vaginosis or the presence of organisms related to bacterial vaginosis, as the organisms can increase rates of HIV replication. There are also implications for perinatal transmission of HIV: in 343 women from Malawi, perinatal HIV transmission doubled from 14% in women with normal vaginal bacteria to 28% in women with bacterial vaginosis.

Bacterial vaginosis can be treated, using metronidazole in an oral formulation or applied to the vagina in gel form. Clindamycin, another effective treatment, is available in oral or vaginal cream formulations. Treatment recommendations are the same for HIV-positive and HIV-negative women.

Yeast Infections

About 75 % of all women experience a yeast infection at some point in their life, and 5% experience chronic recurrences. Symptoms of yeast infections include itching, pain or difficulty urinating, and thick, white vaginal discharge. The prevalence of yeast infections is not significantly different in HIV-positive women, except in women who are severely immunocompromised, but HIV-positive women are more likely to have oral and rectal yeast colonization than HIV-negative women.

Of concern to providers is the increasing number of yeast infections caused by non-albicans strains of candida. Infections caused by non-albicans strains are harder to treat, as they are resistant to most commonly available treatments. The higher incidence of resistant strains can be attributed to the over-use of single-dose treatments for yeast infections and over-the-counter treatments. In HIV-positive women, the incidence of non-albicans strains is about 25%, and there is controversy as to whether this is the same as or higher than the incidence in HIV-negative women, as studies have shown conflicting results.

Several considerations should be made when treating HIV-positive women for yeast infections:

- Topical therapies (creams) will be most effective if seven-day treatments are used;
- Practitioners should consider using anti-fungals prophylactically when antibiotics are used to treat other infections;
- There are drug interactions between ketoconazole (Nizoral) and indinavir (Crixivan), ritonavir (Norvir) and nevirapine (Viramune). Ketoconazole can increase indinavir levels

by 68%, and ritonavir can increase ketoconazole levels to three times the optimal levels. Ketoconazole and nevirapine should not be used together, as ketoconazole levels decrease by 63% and nevirapine levels increase by 15-30%.

An interesting study by Cassone and colleagues showed that the combination of ritonavir (Norvir) and indinavir (Crixivan) inhibited an enzyme called secretory aspartyl proteinase (SAP), which is produced by candida and contributes to its virulence. The ritonavir/indinavir combination had therapeutic effects in candidiasis similar to fluconazole (Diflucan), a common treatment agent.

Trichomoniasis

Trichomoniasis ("trich") affects 2-3 million American women annually, with an incidence rate in HIV-infected women of 10-17%. Trich is usually transmitted sexually, and its symptoms include vaginal itching, yellowish-green vaginal discharge, redness of the vulva and/or vagina, painful intercourse, abdominal pain, and painful urination. Half of infected women may also experience no symptoms (but left untreated, the infection can progress to pelvic inflammatory disease). A single dose of metronidazole (Noritate) is effective for curing the disease, and cure rates are up to 90% if a woman's sex partner is treated simultaneously. Treatment recommendations for HIV-positive and HIV-negative women are identical.

There is an interesting relationship between HIV transmission and trichomoniasis. Secretory leukocyte protease inhibitor (SPLI), a substance that is believed to protect the cells of the mucous membrane of the vagina from HIV infection by inhibiting HIV protease activity, is degraded by trichomoniasis, increasing HIV transmission risk.

Human Papilloma Virus (HPV)

It is estimated that more than 50% of sexually active adults are infected with one or more strains of human papilloma virus (HPV). The virus is transmitted by direct contact, and is usually latent after infection. When HPV is expressed, resulting conditions range from genital warts to cancer.

The HIV Epidemiology Research Study (HERS), a surveillance study involving 800 HIV-positive women and 400 matched controls, showed that 66% of HIV-positive women are co-infected with HPV, compared to 34% of HIV-negative women. Another study by Palefsky and colleagues showed that an HIV-positive woman with a CD4 cell count less than 200 is more likely to be infected with HPV than an HIV-positive woman with a CD4 cell count greater than 200 . Additionally, the expression of latent HPV is directly related to an individual's degree of immunosuppression. The ratio of latent to active HPV in the general population is 8:1, but is 3:1 in HIV-positive women with CD4 cell counts greater than 500 and 1:1 in HIV-positive women with CD4 cell counts less than 500.

Another striking difference in HPV between HIV-negative and HIV-positive women is in the persistence of the virus in the two groups. Generally, HPV infections are transient, lasting for about 8 months. Persistent high levels of HPV have been linked to CIN - abnormal cells in the cervix. In a study comparing 220 HIV-positive women and 231 HIV-negative women, 24% of the positive women had persistent HPV, compared with 4% of the negative women.

Regular pap smears are essential for detecting abnormal cells and preventing cervical cancer. A pap smear is a simple procedure in which a physician obtains cells from the surface of the cervix, using a special brush to collect a sample of cells from the area where most cancers begin to develop. The cells are placed on a slide and are examined with a microscope to check for abnormalities. The cervical pap smear is the only cancer screening test in the world that has decreased both the number of cases of a cancer and the number of deaths related to a cancer.

Approximately 25-40% of pap smears performed on HIV-positive women are abnormal, a rate about ten times higher than that of HIV-negative women. There are various abnormal results:

ASCUS - stands for atypical squamous cells of undetermined significance. Persistent ASCUS results are often further evaluated by a physician through a process called colposcopy. A colposcopy is a magnification of the cells of the cervix in order to pick out cells to biopsy to determine if any cancerous cells are present.

Dysplasia - occurs when cervical cells undergo a series of changes in their appearance. The cells look abnormal under the microscope, but they do not invade nearby healthy tissue. There are three degrees of dysplasia, classified as mild, moderate, or severe.

HSIL/LSIL - SIL stands for squamous intraepithelial lesion. HSIL describes high-grade SIL, while LSIL describes low-grade SIL. A squamous intraepithelial lesion is another term that is used to describe abnormal changes in the cells on the surface of the cervix. HSIL indicates a large number of precancerous cells, while LSIL describes early changes in the size, shape, and number of cells.

CIN - is another term that is sometimes used to describe abnormal cells. The term CIN, along with a number (1 to 3), describes how much of the cervix contains abnormal cells.

Carcinoma in situ - describes a pre-invasive cancer that involves only the surface cells and has not spread into deeper tissues.

Cervical cancer, or invasive cervical cancer, occurs when abnormal cells spread deeper into the cervix or to other tissues or organs. Invasive cervical cancer was added to AIDS indicator conditions in 1993.

Common therapeutic options for LSIL include local excision (cell removal); careful observation; cryosurgery (use of liquid nitrogen to freeze tissue to extremely low temperatures, thereby killing the tissue); laser therapy (destruction of abnormal cells with a light beam); LEEP (removal of the top layer of cells on the cervix, followed by an examination to determine if the cells are cancerous); electrocautery - (removal of lesions using electric current to generate heat). For HSIL, therapeutic options also include conization (removal of a cone-shaped piece of the cervix) and hysterectomy (removal of the uterus). Even with these treatments, HIV-positive women are more likely to have recurrences of HSIL/LSIL than their HIV-negative counterparts.

Dr. Anderson concluded her presentation by reviewing recommendations for the management of gynecological concerns for women with HIV. In the first year after HIV diagnosis, two pap smears should be performed, and if both are normal, pap smears should be performed annually. Any HIV-positive woman with a previous abnormal pap smear, a history of HPV infection, treatment as described above for an abnormal pap smear, or with AIDS, should continue more frequent pap smears (every four to six months). Additionally, it is recommended that HIV-positive women who have a pap smear indicating dysplasia or SIL undergo colposcopy. Some practitioners have advocated routine colposcopy as an additional preventative measure.

Anne Monroe is research associate at Cornell's Clinical Trials Unit in New York City and a writer on HIV/AIDS topics.

Special Delivery: HIV and Pregnancy

by Jill Cadman

The significant reduction in the rate of transmission of HIV from mother to child (vertical transmission) is one of the true success stories in AIDS research today. In many industrialized

nations, rates of transmission have dropped substantially to below 5%. Success has been more difficult to attain in the developing world, where traditional obstacles to care and treatment impede the implementation of sometimes costly and complex interventions aimed at preventing vertical transmission.

While the number of HIV-infected infants born in the US has decreased to an average of 200 to 300 per year, the number of babies infected worldwide through vertical transmission and breast-feeding is projected to reach 700,000 in 1999. However, recent studies indicate that simpler, less expensive interventions more appropriate to resource-poor countries are also effective. In addition, efforts to address other risk factors associated with vertical transmission have revealed more information on the roles of breast-feeding, maternal viral load and elective cesarean sections.

Preventing Transmission using AZT

The landmark clinical trial ACTG 076 demonstrated that a three-part course of AZT treatment (administered before birth orally, during labor with an IV infusion, and to the newborn orally) reduced the rate of vertical transmission by two thirds, from 25% to 8%. While this regimen has become the standard of care in industrialized countries, it is not economically feasible for use in the developing world. Researchers have been evaluating abbreviated courses of treatment overseas that may be more affordable and practical.

A recent trial performed in a non-breast-feeding population in Thailand studied the use of AZT beginning in the last month of pregnancy: at week 36, as opposed to week 14 in the 076 regimen. During delivery the drug was administered orally, not intravenously, every three hours. No drug was delivered to the newborn. This simplified short course regimen resulted in an impressive 51% reduction in the rate of vertical transmission from 18.9% to 9.4%.

It may be possible to delay AZT treatment even longer and still achieve significant improvements in the rate of vertical transmission. A chart review of 939 HIV-exposed infants conducted by the New York State Department of Health demonstrated that even when treatment did not begin until labor, transmission of HIV was often prevented. The rate of vertical transmission was also significantly reduced when AZT was administered only to the infants, beginning within 48 hours postpartum.

When treatment was begun during pregnancy, the rate of vertical transmission was 6.1%, when begun during labor and delivery, the rate was 10% and when begun within the first 48 hours of life, the rate was 9.3%. In the absence of AZT treatment, the rate of vertical transmission was 26.6%. In the U.S., the standard of care remains the full three-part 076 protocol, which has the greatest potential to reduce vertical transmission. However, the results of this study indicate that it is still worthwhile to initiate AZT therapy during labor and delivery, or immediately after birth, regardless of perinatal treatment.

Judging Nevirapine

The short course Thai regimen costs about \$70 per intervention (with a price reduction from the drug manufacturer), significantly less than the full 076 regimen, which costs \$800. However, many developing countries spend an average of only about \$5 per person annually for healthcare, effectively putting even the short course treatment out of range of the vast majority of women in resource-poor areas. In response to this, HIVNET 012 was undertaken. This study showed the benefits of only two doses of nevirapine (viramune) - one to the mother and one to the infant - in decreasing the rate of vertical transmission.

Nevirapine has several important advantages over AZT. It is a rapidly acting drug because, unlike AZT, it does not need to be metabolized before becoming active. Nevirapine crosses the placenta very quickly and reaches therapeutic levels in the fetus within 30 minutes of administration to the

mother. Nevirapine also has an extremely long half-life (the time required for half the quantity of a drug to be metabolized) of 46 hours in the newborns and 61 hours in the mother. A possible drawback to the use of nevirapine is the potential for rapid development of HIV resistance to the drug.

Results of the HIVNET 012 study were reported in September at the Second Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants in Montreal. The trial, conducted in a breast-feeding study population in Uganda, compared the efficacy of short course AZT versus nevirapine in 626 HIV-positive pregnant women. The nevirapine regimen consisted of a single 200 mg oral dose at onset of labor and a single 2 mg/kg dose to the infant within 72 hours of birth. The AZT regimen included an oral loading dose of 600 mg administered at the onset of labor followed by 300 mg administered every three hours until delivery and one week of 4 mg/kg AZT twice daily for the infant.

The drug coverage period of the two regimens was equivalent because of the long half-life of nevirapine. A single dose given to the mother and infant maintained the nevirapine at therapeutic levels for at least seven days. This is similar to the one week of exposure in the infants receiving the AZT regimen, which has a much shorter half-life, requiring twice daily dosing for seven days (assuming that the mother is giving her baby the prescribed dose).

The HIV infection rates at three days of age were essentially equivalent in the two groups: 8.2% in the nevirapine arm and 10.4% in the AZT arm. However, at 6-8 weeks of age, the difference in the rate of transmission was statistically significant between the two treatment groups: 11.9% for nevirapine and 21.3% for AZT. The benefit persisted, and by 14-16 weeks the difference had increased, with a 13.1% rate of transmission in the nevirapine group and a 25.1% rate in the AZT group. The efficacy of nevirapine when compared to AZT was 47% greater. Both drug regimens were well tolerated.

Brooks Jackson, MD, US Chair of the HIV NET 012 study, noted that, in addition to being safe and effective, the advantages of the double dose of nevirapine are that it is affordable and applicable for developing countries. The nevirapine regimen costs about \$4 per mother/infant pair. Dr. Brooks stated, "We view this as very exciting and really the first intervention that I think will be able to be widely implemented in developing countries."

The Role of Breast-Feeding

In industrialized countries, it is not recommended that HIV-positive women breast-feed their infants, as this is a known route of vertical transmission. However, breast-feeding continues in many parts of the developing world due to lack of affordable and safe infant formulas. Breast-feeding can provide protection against diarrhea, respiratory disease and malnutrition. Mothers who do not nurse their infants may be stigmatized in their communities.

However, breast-feeding limits the potential of short course antiretroviral regimens in minimizing rates of vertical transmission in the developing world. The Thai short course AZT regimen mentioned above achieved a 50% reduction in vertical transmission in a non-breast-feeding study population. When this same regimen was evaluated in the Ivory Coast and the mothers were permitted to breast-feed, the efficacy fell to 30% by the time the babies reached 450 days of age.

Recent studies report that breast-feeding increases the risk of HIV transmission from mothers to babies by as much as to 16%. In 1999, over 200,000 babies are projected to become infected with HIV through breast milk. In view of the obstacles to the elimination of breast-feeding among HIV-positive women in developing countries, approaches to preventing transmission were recommended at the Montreal conference. These included providing antiretroviral therapy during breast-feeding, preventing HIV seroconversion in HIV-negative mothers during breast-feeding, treating breast sores and other infections, such as mastitis, in the mother and mouth sores in the

infant, Vitamin A supplementation in the mother and possibly avoiding mixed feeding (combining breast-feeding and formula feeding).

A study reported at the conference documented that alternatives to breast milk can be successful when provided to women in developing countries. The first head-to-head comparison of the effects of formula feeding versus breast-feeding was conducted in Kenya. All women had access to treated municipal water and received instructions on proper infant feeding techniques. Adherence was 96% with breast-feeding and 70% with formula feeding. At 24 months, the rate of HIV infection was 20.5% in the formula group and 36.7% in the breast-feeding group. Transmission via breast milk was highest in the first week of life and by six months of age, 75% of breast milk infections had already occurred. At 24 months of age, mortality rates were comparable between both arms (24% for breast-fed infants versus 20% for formula fed).

Viral load, Transmission and HAART

Another important factor in the risk of vertical transmission is maternal viral load. Many studies have reported that women with high viral loads transmitted the virus more often than women with low viral loads. The investigators of the clinical trial, ACTG 185, found that the risk of transmission was lowest in women with fewer than 500 copies of HIV. There were no cases of vertical transmission among women with undetectable viral loads. However, transmission occurred at all levels of detectable HIV.

This finding underscores the importance of treatment strategies aimed at reducing viral loads. Lynne Mofenson, MD, the study's principal author, stated, "In addition to improving a woman's overall health, reducing the level of HIV may also reduce a woman's chance of giving birth to a child with HIV infection." Dr. Mofenson cautions that although none of the women in this study transmitted virus to their children, there have been reports of transmission even from women who had undetectable viral levels.

Although opinions vary, there is a consensus that HIV-positive pregnant women should be treated with regimens that would not be considered substandard in non-pregnant women. However, AZT monotherapy is still the official recommendation for management of HIV-positive women whose health status is such that therapy would not normally be indicated. In actual practice, the use of antiretroviral therapy during pregnancy is changing. An analysis of data on 1,202 pregnant women in the WITS study indicated that, today, approximately one third of women in this study population still receive AZT monotherapy. AZT and a second antiretroviral, usually 3TC, are used by another third and the remaining 33% are being prescribed HAART regimens.

The average viral load in women in the WITS study who transmitted the virus to their babies was nearly three times higher than the average viral load of women who did not. In addition, the use of AZT therapy was significantly associated with a lower rate of vertical transmission, although treatment with AZT was not associated with decreased maternal viral load. Lead author Patricia Garcia, MD, notes, "This supports previous studies that found AZT therapy during pregnancy reduces the risk of perinatal transmission, but not solely as a result of reduction in maternal HIV levels. The same may not be true for combinations of potent antiretroviral drugs that are capable of reducing maternal viral load to undetectable levels."

Since HAART achieves the goal of reducing HIV viral load to undetectable levels and viral load is a significant factor in vertical transmission, it may be a good choice for HIV-positive pregnant women who have access to therapy. However, there is limited experience using these drugs during pregnancy, and their possible benefits must be weighed against the lack of information on potential long-term effects of children exposed to them.

Elective Cesarean Sections

Since a large proportion of vertical transmission occurs at or near delivery, intervention at this

time might prove beneficial. Elective (non-emergency) cesarean section prior to the time the mother's water breaks can prevent the infant from being exposed to maternal blood and secretions. In an analysis of over 8,000 women, risk of vertical transmission was reduced by over 50% with elective cesarean section compared to other modes of delivery. In women who received antiretroviral therapy, the rate of transmission was 2% with elective cesarean section and 7.3% with other modes of delivery. In women who were not on antiretroviral therapy, the transmission rates were 10.4% with elective cesarean and 19% with other modes of delivery. Data for this analysis were obtained at a time when HAART was not available. Therefore, there is no information as to whether elective cesarean sections would provide any added benefit for women on HAART with undetectable viral loads.

As a prevention intervention, antiretroviral therapy is clearly a better option than elective cesarean section, as treatment during pregnancy may prevent transmission in the prenatal period and also provides post-exposure prophylaxis to the infant. An elective cesarean section may be beneficial in the following scenarios: women who have not taken antiretrovirals during pregnancy; women with persistent or rising viral loads; and women with difficulty adhering to HAART.

Current US Public Health Service Guidelines do not recommend universal cesarean sections in HIV-positive pregnant women. Instead, women should be apprised of all available information and individualized decisions should be made jointly between the physician and the patient.

Since cesarean section is major surgery, there are associated complications for the mother. While cesarean sections are generally quite safe in industrialized countries, some studies have found that HIV-positive women have an increased risk of post-operative complications. Furthermore, surgical procedures may not be an option for the majority of women in resource-poor countries with limited health care infrastructures and budgets.

Conclusion

Vertical transmission is considered by some to be a preventable occurrence. In order for all women to benefit from the advances that have been made in this field, major initiatives are needed to provide education, health care, treatment and empowerment to women. Effective interventions applicable in the developing world have been developed, but it remains to be seen if even these simplified regimens can be widely implemented. As Mark Wainberg, PhD, Co-Chair of the Conference on Global Strategies for the Prevention of HIV Transmission stated, "We now have the scientific ability to make a difference. Does the world have the will to translate scientific achievement into practical success?"

Jill Cadman is a ACRIA board member and a research associate at the Bentley-Salick Medical Practice in New York City.

Women in Clinical Trials

by Anne Monroe

It's important for women to enroll in HIV clinical trials. And at a time when 31% of new U.S. HIV infections are in women, and women account for about 17% of AIDS cases overall, it's more important than ever. HIV-infected women must be represented in clinical research in order to insure the availability of accurate information regarding side effects and pharmacokinetics in women as the face of the epidemic changes.

Both the Adult AIDS Clinical Trials Group (ACTG) and Community Programs for Clinical Research on AIDS (CPCRA) have included women in their trials since their inception. The overall enrollment of women as of 1997 was 19 percent of the adults in the CPCRA and 15 percent of

those in the ACTG. The pharmaceutical scorecard has not been as impressive. In an attempt to bolster access for women to pharmaceutical-sponsored trials, the FDA proposed a rule that would permit the agency to place a study on hold if it unnecessarily excluded women or any other group. This "clinical hold" rule has not been adopted, but merits attention, as it promotes equal access to investigational medications and recognizes that women have the right to make decisions regarding their individual health in the face of HIV infection.

So what can we do immediately to encourage women to enroll in clinical trials? At the 1999 Conference on Women and HIV/AIDS, several sessions and poster presentations focused on the underrepresentation of women and proposed ways to increase women's participation in both pharmaceutical- and government- sponsored trials. Drs. Howard Edelstein and Susan Jacobson of the Family Care Network, a San Francisco Bay area consortium of agencies providing HIV care, initiated a surveillance study to gather information regarding barriers to women's enrollment in clinical trials. The survey was based on the assumption that both structural and attitudinal barriers exist that prevent women from enrolling in clinical trials. In order to identify those barriers, 101 HIV-positive women not enrolled in clinical trials and 40 women enrolled in clinical trials were interviewed. The primary care providers of the unenrolled women were also interviewed.

Among the women not enrolled in clinical trials, reasons for not participating included lack of information about clinical trials, lack of interest in participating, and fear of side effects. Interestingly, childcare, transportation, and amount of time required for participation were not cited as reasons for not participating.

Among the women enrolled in clinical trials, the greatest facilitator to participation in a trial was the support and/or recommendation of the primary care provider. Women enrolled in trials also identified the support of the research staff as a major facilitator to participation. Difficulties in participating in a study, cited by fewer than a quarter of the women, included amount of time required to participate and lack of transportation.

From the provider's side, perceived barriers to participation included gender prejudice in the medical profession, lack of knowledge about available studies, and lack of coordinated care. Although 48% of providers surveyed considered their patient to be a good candidate for a clinical trial, only 14% had discussed the option of participation in a clinical trial with that patient. Considering the importance that participants placed on their provider's recommendation to participate in a clinical trial, providers must have a vested interest in increasing the enrollment of women and translate this interest into action by referring their female patients to clinical trials.

Kids Korner: Pediatric Treatment

by Tim Horn

Our ability to drastically reduce mother-to-child HIV transmission rates is good news indeed. But try explaining such good fortune to the estimated 10,000-plus children in the United States who are already infected with the virus. Yet, as we have been seeing with adults infected with the virus, controlling HIV in our youngest patients has gotten dramatically better over the last few years. Ten years ago, a pediatric HIV diagnosis was associated with a dismal prognosis: most infected children would die before their fifth birthday. Today, thanks to early access to care and triple-drug therapy, approximately half of all HIV-infected children will live to enter-and graduate-from high school and beyond. And with more information quickly emerging with respect to how HIV-infected children should be treated, we can expect the success rate to improve significantly.

Pediatric HIV Disease

Contrary to popular opinion, children are not simply mini-adults. HIV, even during the earliest

stages of infection, can severely affect a child's development, whether it be physical growth, psychological involvement, or emotional well-being. A child's immune system is also different from that of an adult's; HIV rapidly impairs its ability to control common childhood infections, such as bacterial-associated lung and ear infections and viral infections such as chickenpox. HIV also prevents the immune system from producing memory cells which, in adults, help ward off life-threatening infections like pneumocystis carinii (pneumonia), mycobacterium avium complex (MAC), and cytomegalovirus (CMV). Adding insult to injury is the fact that many HIV-infected children are born to mothers who abused alcohol and/or drugs while pregnant, which can exacerbate the problems associated with HIV considerably.

Researchers have shown that HIV-infected babies tend to have higher viral loads than adults, which can sometimes reach millions of HIV-RNA copies in a single milliliter of blood. As a result, the lessons we have learned treating adults with HIV hold true for children infected with the virus: a powerful combination of drugs should be used to lower children's viral loads to the lowest possible level.

Treating Pediatric HIV Infection

The United States Public Health Service-the federal agency that oversees all that is health- and medical-related in this country-has issued guidelines regarding how best to treat HIV-infected children. This, as Martha Stewart would say, is a good thing, as federal guidelines are the greatest tool we have in making sure that all HIV-infected children are sufficiently cared for and treated.

The Guidelines-which are updated regularly and published by the Centers for Disease Control (CDC)-are based on data collected from clinical trials. We know that anti-HIV drugs, particularly when used in combination with each other, work well in children. In a study looking at nevirapine (Viramune) in combination with AZT (Retrovir) and ddI (Videx) in eight infants aged two months to 16 months, the drugs succeeded in reducing viral load by 97% after four weeks of therapy. And, after 14 months, 2/8 (25%) infants studied.

Anti-HIV drugs are absorbed, metabolized, and eliminated from the body differently in children than in adults. In turn, various research teams have spent the better part of the last four years figuring out the correct dosages for each anti-HIV drug for children infected with the virus. At the present time, eight of the 15 drugs approved for adults are also approved for children. See Table on page 6 for more about drugs available in kid-friendly liquid/powder formulations and the doses of each compound used to treat pediatric HIV infection.

Preventing Opportunistic Infections

As with adults, HIV-infected children need to take preventive therapies (prophylaxis) to ward off common-childhood and AIDS-related infections. All children less than one year of age must take Bactrim or Septra (TMP/SMX)-or if they cannot handle those drugs, either dapsone or aerosolized pentamidine-to prevent pneumocystis carinii pneumonia (PCP). Children between the ages of one and two should take PCP prophylaxis if their CD4+ cells fall below 750. Two- to five-year olds with CD4+ cell counts below 500 should also be taking prophylaxis, as should all children six years or older with CD4+ counts below 200 cells/mm³ (similar to adult recommendations).

A rather unique HIV-related problem among children is lymphoid interstitial pneumonitis (LIP). Simply put, LIP is caused by a hyperactive immune response to a usually harmless infection in the lungs. The symptoms are similar to those of asthma (e.g., coughing, wheezing, shortness of breath, tightness in the chest) and, likewise, is treated with corticosteroids like prednisone, and with breath-restoring inhalers.

Onwards and Upwards

While data certainly suggest that triple-drug anti-HIV therapy has made a tremendous impact on the lives of children living with the virus, it's not yet entirely understood to what extent these powerful drugs affect their young immune systems. In turn, maintaining children on prophylaxis remains the standard of care and it is still not clear whether or not immune system-related complications such as LIP are less likely to occur during successful anti-HIV therapy. Only time will tell. Luckily, HIV-positive children have a lot more of it to go around.

Tim Horn is the executive editor of The PRN Notebook, published by Physicians' Research Network in New York, and a member of ACRIA's Research Advisory Committee.

Re-examining Treatment Recommendations for Women

by Kathryn Anastos, MD

HIV infection in the United States has increased among women and individuals of color, while decreasing among white men. Women and individuals of color now represent 67% of people newly diagnosed with AIDS, 62% of individuals living with AIDS, and 69% of newly reported diagnoses of HIV infection. The highest rates of AIDS, of HIV-infection and of HIV-related deaths are among African American women and men. Nearly 80% of HIV infected women in the United States are African American or Latina. It is thus extremely important to know if the recommendations for treatment of HIV infected people, developed almost entirely from data in white men, are valid for women and individuals of color.

In the last year, new information has become available suggesting that the "natural history" of HIV-infection, that is, the way in which HIV can make people sick, may be different in women and in people of color, compared to white men. However, the recommendations followed by doctors to determine treatment for individuals with HIV-infection are based mostly on the results of studies of viral load and treatment in HIV infected white men. There are three areas in which there is evidence of differences between women and men. These include levels of viral load, T-cell counts in people with or without HIV infection, and the level of T-cell counts at which AIDS develops. The differences found between whites and people of color include viral load differences and differences in how fast T-cells decline.

There are now several studies in the United States which investigate the natural history of HIV infection in women. Two large studies include only women: the Women's Interagency HIV Study (WIHS), which has enrolled 2,059 HIV infected women and 569 HIV uninfected women, and the HIV Epidemiology Research Study (HERS), which includes about 800 HIV infected and 400 HIV uninfected women. Some studies include both men and women, usually with about four times as many men as women. This includes the ALIVE study (AIDS Link to Intravenous Experience) which follows the course of disease in women and men enrolled in a drug treatment program in Baltimore. Nearly all (96%) of the ALIVE participants are African American.

Recent studies suggest that viral load tends to be lower in women compared to men, in people of color compared to whites, and in those participants reporting a history of injection drug use. In addition, some data has suggested that for women with HIV infection, remaining alive is predicted better by the T-cell count than by the viral load. These findings have led some physicians and scientists to question whether it is appropriate to assume that the information gained from studies of white men should be used to develop the treatment recommendations for women and people of color.

In November of 1998, researchers from the ALIVE study published findings about the viral load levels of the women and men in the study. At every level of T-cells, the viral loads for the women were lower than in the men. For example in women the average level of viral load was 3,000 (copies/ml of blood) but in men it was 9,000. Similar results had been reported about a year earlier in a much smaller group of HIV infected women and men in the US military. In early 1999, the WIHS investigators also presented results which compared the viral loads in the WIHS women to the viral loads among the men in the Multicenter AIDS Cohort Study (MACS). These results indicated that the viral loads in women were 20% lower than in the men at any given level of T-cells. This information prompted other researchers to look at viral loads in women and men: some have found that there is a difference, and some have not found such a difference. The WIHS and MACS investigators also found that the viral load in people of color was 35% lower than in whites, an even larger difference than they found between women and men.

Although it is not often discussed, it has been known for some time that the "normal" T-cell levels in women and men are different. In people without HIV infection, the T-cell levels are about 100 cells higher in women than in men: on average, in people without HIV infection, women's T-cells are about 1100, and men's are about 1000 (cells/cubic mm of blood). This gender difference in T-cell counts is important when interpreting study results, as study groups of HIV infected individuals are often stratified by T-cell count in an attempt to adjust for duration of infection. It is assumed that people with similar T-cell counts have been infected for the same amount of time. That assumption may be incorrect when comparing groups of women and men. One study has shown that in people infected with HIV, the T-cells in the women remained about 100 cells higher than in the men for at least the first five years of infection. T-cells counts do not appear to differ by race however, at least across the Caucasian, African-American, and Latino groups in the United States.

The differences in T-cells may matter if they mean that women can develop AIDS or HIV related diseases at higher T-cell counts than in men. Alternatively, women's higher T-cell counts may "protect" them by preventing the development of AIDS for a longer period of time after becoming infected with HIV. Unfortunately, there are few studies that can help answer these questions, which are best answered in a study which includes people whose date of infection with HIV is known, or who have been followed for a long time before they develop AIDS. Most studies which have looked at gender differences in disease progression have followed people who are stratified by T-cell counts, as described above. Some studies have found no difference, some have found that women progress faster, and others have found that men progress faster. There is no study, however, that has been designed to answer this question, and the available data really leave the question unanswered. However, a very recently published study of a group of HIV infected women and men in Europe, had some disturbing findings. The investigators, using mathematical modeling of T-cells, demonstrated that the women developed AIDS at higher T-cell levels than the men.

Similarly, there is very little information to tell us if there is a difference in clinical disease between whites and people of color. Most studies have found no difference in rates of disease progression or death by race. However, the MACS study (a study of men only), which includes very few men of color, found that the rate at which the T-cells fell was much slower in the men of color compared to the white men-suggesting that the men of color may do better clinically. Similarly, the WIHS investigators have preliminary findings that T-cells may fall more slowly in African American and Latina women, compared to white women.

There are three major measures that physicians or other providers use to recommend treatment to HIV infected individuals. These are: clinical disease (if the HIV infection is making the person sick), the T-cell count, and the viral load. It is clear that highly active antiretroviral therapy (HAART) should be recommended and provided to any person with clinical disease. It is less clear at what T-cell or viral load level treatment should be first recommended. The current recommendation is that HAART be recommended for any HIV infected person whose T-cells are

less than 500 cells/mm³, or whose viral load is higher than 10,000 to 20,000 copies /ml. Although most people would not develop clinical disease at these high T-cell and low viral load levels, the purpose of treating early is to prevent the development of clinical disease. Because of the recent information suggesting gender and racial differences in T-cells and viral load, there has been concern that these recommendations may not be correct for women and people of color. However, two things must be kept in mind when considering changing the recommendations.

First, because of their lower viral loads when treatment is initiated (usually because of T-cell levels below 500 cells), it may be that women and people of color respond better to antiretroviral therapy. If this is the case, then the current recommendations may be appropriate, or it may even be that treatment could be initiated later for women and people of color. What is most important clinically is how different groups respond to treatment, not whether their viral loads are different in the absence of treatment. It is thus critically important to determine if the differences in viral load mean that women and people of color do better with treatment than white men, or worse. The scientific community is only beginning to be able to answer this question. Much more research is required.

Second, it is unclear whether the current treatment recommendations are "correct " even for white men. HAART has not been around long enough for us to know if people treated when the T-cells fall below 500 cells do better in the long run than people who wait until the T-cells fall below 350 or 300 cells/mm. A recent study from Europe found that HAART was initiated at lower T-cell counts in people with a history of injection drug use or who had completed less schooling, but, these groups were not any more likely to develop AIDS. This suggests that people who initiate treatment later may do just as well as those who initiate treatment by the current recommendations. Again, the optimal time to initiate treatment remains unanswered for all HIV infected individuals. It is thus premature to suggest a change in treatment recommendations for specific groups. It is not clear whether such a change would mean women or men of color would be treated earlier or later. Investigations of this question should clearly include enough women, and men of color, to allow informed decision making for those groups specifically.

In summary, much recently published information suggests that there are gender and/or racial differences in T-cell counts and in HIV viral loads. However, it is unclear whether these differences indicate that there are clinical differences by race or by gender, even in people not taking any treatment. The most important question is whether these differences in T-cell and viral load levels mean that treatment would be more or less effective in delaying or preventing clinical disease, including AIDS, for women and people of color. More study is needed to determine this.

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Microbicides

by Anna Forbes and Polly Harrison, PhD

All over the world, consistent condom use is difficult to achieve, especially within long-term relationships. Because of cultural issues, embarrassment, low self-esteem, financial dependency and/or domestic violence, millions of women simply can't or don't insist on male condom use. In studies done on the subject, consistent condom use is rarely reported by more than 50% of those surveyed. Most surveys of heterosexual primary partnerships show that condom use happens 20% of the time or less. The only studied populations that have reported using condoms regularly for more than half of their acts of intercourse are sero-discordant couples and commercial sex workers. For sex workers, who may get paid more if they don't insist on condom use, economic

need may often overwhelm their need for self-protection. Even individuals who regularly use condoms with "outside" partners have proven unwilling or unable to use them with their primary partners. And, in cultures in which childbearing is directly linked to a person's self worth, the prospect of childlessness often outweighs the risk of HIV infection in women's minds.

All in all, a woman's ability to refuse to have sex without a condom usually depends more on other factors in her life than on her perceptions of HIV risk.

According to the Joint UN Programme on AIDS ("UNAIDS"), unprotected sex with an HIV-positive man is by far the leading cause of HIV infection among women, and the result is that more women than men are now getting infected with HIV annually. Since a woman's ability to use condoms ultimately depends on the cooperation of her male partner, this number is likely to increase. Even the internal or "female" condom is visible when in place and, thus, is not a method most women can use without their partner knowing. What is needed is an easily accessible, inexpensive, safe, effective prevention method - "non-condom alternatives" that would give the millions who can't or don't insist on condoms a way of protecting themselves from HIV and other sexually transmitted diseases (STDs).

Every day, 6,300 additional women worldwide contract HIV and hundreds of thousands more are infected with other sexually-transmitted diseases. In developing countries, STD's excluding HIV are the second leading cause of illness, disability and death among women of reproductive age. In the United States, there are 15 million new cases of "non-HIV" STDs each year, the majority in women, most under age 24 and many in their teens. According to government estimates, by 2010 at least half of all Americans infected with HIV will be women. In fact, in some parts of the country, we're there already. In Florida, for example, young women constituted 50% of the new AIDS cases reported among people between 13-24 during the years 1995-1997.

Enter "microbicides" - the alternative of the future. Applied in the vagina or rectum, these compounds, in different formulations, will act in various ways to reduce the transmission of STDs, including HIV. While such products are also needed for women and men who have anal sex, virtually all the microbicide research now under way focuses on vaginal use.

So what will these products be like? Similar to birth control products that have been sold over the counter for decades, microbicides could be produced in many forms: suppositories, films, gels or creams inserted with a disposable or reusable applicator, and even sponges or rings inserted into the vagina that release a microbicidal compound slowly over time. Some will be formulated as contraceptive or, for those wanting pregnancy without fear of infection, as non-contraceptive.

Many people want to know, "How does a microbicide work?" This question has several answers. The product leads being pursued work in different ways. Some microbicides work by boosting the body's natural defense systems, others introduce new substances to destroy pathogens or chemically block their entry into human cells, and still others create a type of physical barrier. The most promising products will probably combine several of these approaches. Here are a few examples of microbicides under development:

Antibiotic peptides are small protein molecules that form part of the body's first line of defense against infection. These peptides line every surface of the body-eyes, skin, lungs, tongue and intestinal tract-and kill bacteria within minutes of contact. If applied in concentrated quantities at the site of potential infection, these peptides may kill off pathogens before they infect the body.

Buffer Gel works by maintaining the natural acidity of the vagina in the presence of semen. The healthy vagina is normally about pH 4.2, an environment too acidic for HIV to survive. Semen, however, is alkaline (basic) and during intercourse the pH of the vagina becomes basic, allowing

HIV to survive. Buffer Gel keeps the vagina acidic even during intercourse and creates a physical barrier that inhibits the passage of pathogens into the vaginal and cervical epithelium.

Carageenan is an inexpensive substance derived from seaweed and widely used as a food additive (for example, to thicken ice cream). Carageenan forms a tasteless gel that coats the vagina, possibly preventing HIV from entering the vaginal epithelium. Alternatively, carageenan gel can be formulated with Nonoxynol-9 to make a combination product.

Detergents and surfactants work by disrupting the outer membranes of cells and the envelopes (outer shell) of viruses. This is the mechanism of action of Nonoxynol-9, the active ingredient in most spermicides sold in the United States.

"**Invisible condom**" is how researchers describe non-toxic polymer-based gels that serves as a barrier against viruses and bacteria.

Lactobacillus crispatus (LB) suppository works by re-colonizing the vagina with hydrogen-peroxide producing Lactobacillus. Lactobacillus crispatus is one of many bacteria that live normally in the healthy vagina (a sister species of lactobacilli is found in yogurt). LB helps keep the vagina free from infection by producing hydrogen-peroxide, a substance that is highly acidic. When the ecology of the vagina is somehow disrupted-through infection, douching, or poor hygiene-the LB bacteria can die off, leading to a condition known as bacterial vaginosis (BV).

"**Plantibodies**" represent an innovative approach to microbicide development using genetically engineered plants to produce human antibodies active against a range of sexually transmitted infections (STIs). Antibodies are one of the body's main defense systems, and the basis for vaccine technology. Today, scientists have found ways to isolate the particular antibodies that counteract HIV and other STIs, and to mass produce them relatively inexpensively using genetically engineered plants. This technology raises the possibility of delivering anti-HIV antibodies directly to the vagina, allowing them to combat pathogens before actual infection occurs.

PMPA Gel works in the same way as some of the anti-retroviral drugs currently used for therapy: it interrupts the replication of the virus once it enters cells. The hope is that PMPA (Tenofovir) could be absorbed by cells in the vaginal epithelium and then stop the virus in its tracks once it enters the outer cells of the vaginal wall. Many anti-retroviral drugs that were initially explored as potential AIDS therapies were later abandoned because they could not be absorbed easily into the bloodstream; these same compounds might be perfect candidates for a microbicide because they could be topically applied and not absorbed systemically.

Pro-2000 Gel contains a synthetic polymer that binds to the HIV virus, thereby disrupting binding of the virus to target cells. The gel probably works in a similar fashion to block chlamydia and HSV-2 infections.

The basic idea is that microbicides will also be, like condoms, convenient, simple to use, inexpensive, available without a prescription, and appropriate for distribution in stores, clinics, kiosks and by peer health educators.

It is important to note that microbicides are not expected to be fully as effective against some infections as internal ("female") and external ("male") condoms. Obviously, it is always safer to keep a virus or bacteria from getting into one's body in the first place than it is to try to disable it once it's there. But for those for whom consistent condom use is not an option, an effective microbicide will be much safer than unprotected sex. Couples already using condoms will also benefit from microbicides as something that can be used with a condom for added protection. In the future, some microbicides may also be developed in other formulations such as a mouth rinse

for protection during oral sex, a vaginal wash that can be used by HIV-positive women prior to childbirth as a low-cost way of reducing risk of perinatal transmission, and applications for post-coital use to reduce risk of infection after forced sex or condom failure. And, as better microbicides are developed, they will be designed to be "bi-directional"; in other words, use of a vaginal microbicide will inactivate HIV present in the vaginal secretions, thus protecting her partner, as well as protecting a woman from HIV in her partner's semen.

With concerted, international demand and the kind of financial investment and government priority this critical public health technology deserves, we could have new microbicides on the market within five years. Millions of women and men in all cultures and countries must be able to protect themselves, and condoms just aren't enough. For more information on how you can get involved in advocacy, as an individual or as an organization, please contact the Center for Health and Gender Equity (CHANGE) at 301-270-1182 and ask for Megan Gottemoeller. You can also contact Megan by e-mail at mgottem@genderhealth.org or just drop in on the web site at www.genderhealth.org. For information about what's going on in microbicide research and development, contact Polly Harrison at the Alliance for Microbicide Development at 301-588-8091 or by email at pharriso@aol.com, and take a look at the Alliance web site at www.microbicide.org.

Anne Forbes is the Field Organizer for the Global Campaign for Microbicides and Women-Controlled STI/HIV Prevention Alternatives and Polly Harrison, PhD., is the Director of the Alliance for Microbicide Development in Maryland.

CRIA News

New Trials launched

For much of the second half of 1999, ACRIA's Medical Director, Jerome Ernst, MD, has been working with the Research Department staff to develop new clinical trials that will answer important questions in the fight against AIDS. ACRIA is proud to announce that those efforts are now coming to fruition with several new studies starting as we head into 2000.

We have already begun enrolling two new independent clinical trials. The first examines the dietary supplement SB-300 on diarrhea in HIV positive individuals, the second looks at the use of topical aspirin for painful peripheral neuropathy.

CRIA is also developing another independent trial to explore the naturally occurring compound S-adenosyl-methionine (SAM-e) in treating depression in HIV infected persons. This project is expected to start enrolling shortly.

CRIA will also continue to be a study site for pharmaceutical trials, allowing early access to the newest investigational drugs for a population that might not otherwise be afforded their potential benefits.

For more information on these and other ACRIA studies, please see "CRIA Trials in Progress" on page 2 of this publication or call our Research Department at 212-924-3934, ext. 1.

Hepatitis C/HIV Education Expanded

Recognizing the growing incidence of Hepatitis C Virus (HCV) co-infection in people living with AIDS, ACRIA enlisted our Board member, Douglas Dieterich, MD, in early 1999 to help us create a specialized workshop curriculum on this topic. ACRIA was fortunate to have secured grants in support of the new important education focus from Amgen, Inc., Roche Pharmaceuticals, and Schering Oncology/Biotech.

Most recently, in December, ACRIA received a \$70,000 Ryan White Title I award from the New York City Department of Health to dramatically expand HIV/HCV healthcare education services. Although this is only a three-month contract, it will allow us to teach over 1,000 additional people living with AIDS in New York City about Hepatitis C and the issues surrounding co-infection.

CRIA has hired James Learned to help us accomplish such rapid expansion of HIV/HCV co-infection treatment education. James is among the most experienced educators on treatments for both diseases in the United States. He was a leading provider of treatment education, support and advocacy for clients of the PWA Health Group during the three years prior to 1998, after which he went on to co-found the Hepatitis C Action and Advocacy Coalition in New York City. All of ACRIA's educators will be involved in working with NYC AIDS service organizations to conduct this unique initiative, but James will take the lead on ensuring that the complex healthcare information reaches persons most in need.

New Board Members Elected

CRIA is pleased to announce the election of Vincent Wm. Gagliostro and Kevin Krier to its Board of Directors at the November 17, 1999 Board meeting. These elections mark the culmination of a year when ACRIA realized a significant expansion and strengthening of its governing body.

Vincent is a nationally known artist and graphic designer who has helped mold innovative advertising campaigns of many prominent apparel manufacturers, including Prada, Hush Puppies, and the Gap. Most importantly, Vincent has worked to promote AIDS causes almost from the start of the epidemic. He was a co-creator of ACT UP's "Silence=Death" campaign which was so instrumental in focusing government funds towards AIDS research. Vincent has also been one of ACRIA's most loyal supporters for many years. He has provided our agency with invaluable pro-bono assistance, having created the agency's logo, letterhead, and the design for many of our national publications.

For the past 10 plus years, Kevin has been Principal of Kevin Krier & Associates, which is among the most preeminent international fashion public relations and marketing organization. Kevin has also played a central role in helping the fashion industry support AIDS causes by producing many highly visible charity events, including Todd Oldham and Gucci AIDS Project Los Angeles benefits.

Kevin has been a strong advocate for a variety of AIDS charities in his home base of New York City, including ACRIA's clinical research and HIV treatment education mission. Most recently his firm provided pro-bono assistance to ACRIA by helping Sotheby's organize successful charity auctions for our agency.

CRIA's staff looks forward to the guidance and support which these two new Board Members will provide us in the coming years.

CRIA Hears from its Donors

CRIA has an active Board of Directors, Research Advisory Committee and Community Advisory Board to provide direction of our clinical research and HIV treatment education activities. But we also want to know what ACRIA's supporters think about our performance to date and where our focus should be in the future. To this end, we recently asked our donors to complete a small evaluation form containing both multiple choice rating questions and areas for written comments. Following is a summary of donor responses.

Some donors provided comments indicating that more work by HIV researchers should be conducted in the area of vaccines, on immune reconstitution and on drug regimens which are not so difficult to take.

In the area of HIV treatment education, comments were overwhelmingly positive on the content and quality of this publication, *ACRIA Update*. However, some donors thought that the periodical was too complex to read, that we used language which was more appropriate to the scientific community rather than to lay audiences.

Donors probably made the most comments on what additional topics or regular features they wanted covered by *CRIA Update*. Many respondents wanted us to regularly include a summary of new drugs and other treatments in development, including vaccines. Others wanted specific discussions on prevention efforts, side effects treatments and management techniques, and current statistics on treatment failures.

Probably the greatest disappointment to ACRIA's staff was that many respondents did not yet access treatment information on our web site. However, comments made did not indicate that the site was difficult to use or that the information contained within it was either incomplete or overly complex to understand. Rather, either respondents did not know about the site, did not have a computer or did not have Internet access. For those who use the site, comments on additional treatment information desired were essentially consistent with those made for *CRIA Update* (i.e. more on status of research into new therapies).

CRIA takes all of these comments on our research and education programs seriously and we thank all those who took the time to complete and return our questionnaire.

Much of the donor-stated priorities for ACRIA's research agenda are also high on our Medical Director's list of priorities for future protocols. Studies on certain areas, such as vaccines, require multi-million dollar budgets and unfortunately are not possible for agencies of our size. We would, however, welcome becoming an enrolling site for ongoing vaccine trials. Exploring agents which have fewer side effects and which are easier to take has always been of utmost importance to ACRIA and will continue to be for the life of this agency. Also, we very much want to examine strategies to promote immune reconstitution.

As for our work to educate PLWAs in New York and nationwide, ACRIA has always attempted to provide products and services which meet the needs of a broad and inclusive lay audience. As a result, *ACRIA Update* is written for persons who have little medical background. We will continue to carefully edit articles provided by expert writers with this principle in mind. Additionally, each edition of *ACRIA Update* will continue to cover a major topic of concern to PLWAs nationwide. Those issues identified by donors, such as a drugs in development, will assuredly be covered in future periodicals.