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HIV & Hepatitis Education Prison Project

HEPP REPORT

HIV & HEPATITIS EDUCATION PRISON PROJECT

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INFECTIOUS DISEASES IN CORRECTIONS

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ABOUT HEPP

HEPP Report, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, HEPP Report provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education. HEPP Report is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

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PERTINENT TOPICS ON HIV INFECTION AMONG WOMEN: PREVENTION, LIPODYSTROPHY, AND DRUG-DRUG INTERACTIONS

Bethany Weaver, D.O., M.P.H., Acting Instructor of Medicine, University of Washington Center for AIDS & STD Research (CFAR) and Northwest Correctional Medicine Education Program*

The following sections represent an overview of key points from the 2003 Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the US (available at www.aidsinfo.nih.gov under guidelines, perinatal) and/or the 11th Conference on Retroviruses and Opportunistic Infections (CROI) - February 8 - 11, 2004, San Francisco, CA.

PREVENTION OF VERTICAL TRANSMISSION OF HIV INFECTION

Efficacy of Antiretroviral Therapy

Mother-to-child transmission (MTCT) may be prevented by treating the mother and/or her baby with antiretroviral therapy (ART). Studies have shown a 66% reduction or greater in vertical transmission with different antiretroviral treatment strategies, including both mono- and combination therapy. The first of these studies, initially reported in 1994, showed that the HIV-1 transmission rate for infants who received placebo was 22.6%, compared with 7.6% for those who received zidovudine (AZT). This translates into a 66% reduction in risk for transmission in those who received treatment compared to those who received placebo. Other studies have shown similar results. One study compared nevirapine given to women at the onset of labor and infants at 48-72 hours of life with a very short regimen of AZT given orally during labor and to the infant for the first week of life. In this study, transmission of HIV among the infants at six weeks of age was 12% in the nevirapine arm verses 21% in the AZT arm–a reduction in transmission of nearly 50%. Another study reports transmission rates of 12.3% for nevirapine compared with 9.3% with AZT combined with lamivudine (3TC). In the US, the standard recommendation for infant prophylaxis is six weeks of AZT, regardless of whether the woman has had antepartum, intrapartum, or postpartum ART (for details of AZT dosing in neonates, see perinatal guidelines website noted in the introduction to this article).

It is unclear how intrapartum AZT prophylaxis works as maternal viral load suppression does not fully explain the observed efficacy. The efficacy beyond viral load suppression may be related to the fact that AZT is metabolized into the active triphosphate form within the placenta, which has not been observed with other nucleosides, such as ddI or ddc. Some concerns relating to the safe administration of AZT in pregnancy have been raised with regard to the drug causing disruption in the maternal-fetal barrier, with subsequent observed cytotoxic *in vitro* effects of AZT on the human placenta. However, this has not translated into obvious clinical sequelae in the infant thus far, and the data as presented above do clearly support its use in terms of reduction of HIV transmission to the infant. Whether it relates to increased risk for preterm labor and premature birth, low fetal birth weight, or other more serious clinical events is yet to be determined.

Combination ART appears to have an even greater effect in reducing HIV transmission. In one of these studies, the transmission rate was 10.4% among women who received AZT alone, 3.8% among women who received combination therapy without protease inhibitors (PIs), and 1.2% among women who received combination therapy with PIs. Because of concerns relating to antiretroviral resistance among infected mothers and infants exposed to monotherapy, particularly nevirapine as discussed earlier, the use of combination therapy may be more prudent in the US since it is widely available. Counseling women about the potential for resistance and the long-term effect it may have for her with regard to future antiretroviral options is vital and should be taken into consideration when choosing an appropriate regimen for her. For more detailed information on choosing different strategies in treating pregnant women with HIV infection, please refer to this month's Heppigram on page 4.

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Initial Evaluation and Antiretroviral Considerations for HIV-infected Pregnant Women with Regard to Safety and Toxicity

Initial evaluation of an HIV-infected pregnant woman should include an assessment of HIV-1 disease status, including evaluation of the degree of existing immunodeficiency determined by CD4 count, the risk for disease progression determined by the level of plasma RNA, history of prior or current antiretroviral therapy, gestational age, and supportive care needs, and recommendations regarding options for ART based on the history of previous treatment. The benefits of ART for a pregnant woman must always be weighed against the risk of adverse events to the woman and the baby. These considerations must be carefully thought out and discussed with the patient so that she can make an informed decision. Many women who have begun ART before pregnancy require adjustment of the regimen during the pregnancy due to either (1) intolerance during pregnancy especially in the first trimester, (2) possible dosing changes due to physiologic changes associated with pregnancy, (3) potential long- and short-term effects of the drug(s) on the fetus and newborn, and/or (4) discontinuing agents with potential for reproductive toxicity. As with all pregnant women, those receiving ART should be evaluated and closely monitored for hyperglycemia, anemia, and hepatic toxicity and should be offered optimal nutritional status.

Data are limited regarding the safety of antiretroviral drugs in pregnancy and recommendations for use are based on animal toxicity data, anecdotal experience, registry data, and clinical trials. Data are conflicting as to whether the use of combination ART during pregnancy is associated with preterm delivery. Until more is known, these women should be monitored carefully for pregnancy-related toxicities/complications.

Toxicities related to nucleoside analog drugs, such as symptomatic lactic acidosis and hepatic steatosis, may have a female preponderance, and these conditions have similarities to rare but life-threatening complications in pregnancy, such as acute fatty liver and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). Whether these conditions are increased during pregnancy among women treated with nucleosides is unknown, though there are published case reports that suggest this may be true. The clinician should have a low threshold for considering and screening for any of these mentioned toxicities in a pregnant patient on ART. Among babies born to HIV-infected mothers taking nucleoside therapy during pregnancy, there are conflicting data as to whether these infants are at increased risk for mitochondrial dysfunction, believed to be the etiology behind lactic acidosis and hepatic steatosis. However, this condition, though often fatal when it occurs in infants, appears to be rare.

Regarding the use of non-nucleoside reverse transcriptase inhibitors, the development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women. Hepatic toxicity with systemic symptoms due to nevirapine was 3.2-fold more common in women than men. In a summary analysis from 17 clinical trials of nevirapine use, women with higher CD4 counts (>250 cells/mm^3) were 9.8 times more likely than women with lower CD4 counts (<250 cells/mm^3) to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity. It is unknown if pregnancy increases this risk. At the 11th CROI, it was reported that women were significantly less likely to have an adverse reaction to nevirapine when it was started during pregnancy compared to women not pregnant. However, Martinson, et al reported at CROI that even though use of nevirapine significantly reduced vertical transmission, with HIV occurring in only 8.6% of births among 623 women. Nevirapine-resistant virus occurred in 38.8% of mothers and in 42.4% of infants.

> *"Nevirapine-resistant virus occurred in 38.8% of mothers and in 42.4% of infants."*

Although it is known that PIs are associated with hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes, and diabetic ketoacidosis, it is not known if they increase the risk of pregnancy-associated hyperglycemia, and therefore, glucose levels should be closely monitored in these patients. Please refer to this month's HIV 101 on page 6 for a complete list of currently available antiretroviral drugs with known safety/toxicity information for each drug in pregnancy.

Breastfeeding and HIV Transmission Risk

In the US, breastfeeding among HIV-infected women is not recommended due to risk of HIV transmission, which occurs at a rate of about 7 to 14 percent. According to the World Health Organization's recommendations for MTCP, when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. For information pertaining to appropriate recommended scenarios for HIV-1 resistance testing among pregnant women and mode of delivery relating to vertical transmission of HIV, please refer to the perinatal guidelines cited in the introduction to this article.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry is designed to collect observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of the drugs. The registry does not use patient names, and the staff tracks birth outcome follow-up information. For more information on this registry please refer to resources on page 4.

Clinical Update on Lipodystrophy Syndrome Associated with HIV Infection and Antiretroviral Therapy

The reported prevalence of lipodystropy ranges anywhere from two to 84%, depending on the definition used and the ease of recognition among patients and providers. Tien *et al* reported the estimated incidence of lipoatrophy, or fat loss, and lipohypertrophy, or fat gain, among women with and without HIV infection from the Women's Interagency HIV Study (WIHS). The syndrome is evaluated for by both the participants via questionnaires detailing noticeable body changes and by the researchers via anthropometric measurements at regular intervals. The authors performed a 30-month incidence analysis among 810 women, 605 of whom were HIV-infected and 210 of whom were HIV-uninfected. Overall, among HIV-infected women, the incidence of lipoatrophy was higher (nearly double) than that among the uninfected women after adjusting for age and race, whereas there was no statistically significant difference in central lipohypertrophy seen between the two groups and a lower incidence of peripheral hypertrophy among HIV-infected women. Their findings suggest that peripheral and central lipoatrophy associated with HIV infection appears prevalent among women and that peripheral lipoatrophy in combination with central lipohypertrophy is uncommon.

How different antiretroviral drugs affect the development of lipodystrophy is still largely unknown, though thought to be related most commonly to the use of prolonged PI therapy with or without specific nucleosides or non-nucleosides, such as d4T, ddI, ddc or efavirenz. Murphy et al presented data at CROI suggesting that patients who received DDI plus d4T had an increased risk of peripheral lipoatrophy over four years and that indinavir was associated with lipohypertrophy. In another study reported at CROI evaluating whether changing ART can hasten or alter the lipodystrophy syndrome, the authors reported no effect over 24 months after switching patients from a PI to an efavirenz-, nevirapine-, or abacavir-based regimen.

Important Drug-drug Interactions Associated with Estrogen Use Among HIV-infected Women on Antiretroviral Therapy

Ritonavir has a drug-drug interaction with oral

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contraceptives (OCPs), such as ethinyl estradiol, levonorgestrel, norelgestromin, norethindrone, and norgestrel, in which the level of hormone may be decreased enough to cause contraceptive failure. Thus, this is of consideration in any patient for whom a ritonavir-boosted regimen is being offered. Increasing the dose of OCPs and/or suggesting alternative forms of contraception to the patient may best handle this interaction. The same interaction occurs with amprenavir, though amprenavir levels may also decrease when co-administered with OCPs, thus decreasing the effect of amprenavir and increasing the risk for resistant HIV. For another PI, atazanavir, it is recommended that the lowest effective dose of OCPs be used, as this drug increases the OCP level. It is recommended that no OCPs be used in conjunction with nevirapine due to strong drug-drug interactions. There does not appear to be any significant drug-drug interaction with the use of OCPs and any of the nucleoside reverse transcriptase inhibitors, efavirenz, delavirdine, saquinavir, indinavir, or nelfinavir. Of note, there does not appear to be any significant drug-drug interaction with medroxprogsterone acetate (Depo-Provera®) and antiretrovirals.

Conclusion

The American College of Obstetrics and Gynecology (ACOG) recommends that all women of childbearing age–HIV-infected and HIV-uninfected alike–be offered reproductive health care as part of routine medical treatment. Both incarcerated women and those living in the free world should receive information on birth control options, prevention of sexually transmitted diseases (STDs), prenatal vitamins if a pregnancy is desired, risk factors for HIV infection and other co-morbid conditions should a pregnancy occur, and optimal prevention and treatment of these conditions in order to preserve the overall health of the woman and her baby. Informing incarcerated women about these issues is particularly critical, as they often lack access to care before and after incarceration. In 1995, the United States Public Health Service issued recommendations for universal prenatal HIV-1 counseling and testing, including voluntary counseling and testing for all pregnant women in the US HIV testing of all inmates should be encouraged in correctional settings where reasonable HIV counseling and treatment can be provided. This option affords inmates a chance to make positive changes in their lives and improve their overall health while incarcerated. For women identified as HIV-infected, the focus of care is not only on assessment of her stage of infection and antiretroviral options, but also (1) education regarding HIV transmission risks to her baby during pregnancy and breastfeeding, as well as medical interventions to prevent MTCT (2) helping her understand and cope with realistic expectations for a future pregnancy, and (3) offering effective contraception strategies that will optimize her health before, during, and after such a pregnancy may occur. These are just some of the complex psychosocial issues that an HIV-infected woman may confront. Ultimately, choices impacting her reproductive health are up to the woman alone. As health care providers however, we can facilitate what may be difficult decisions for our patients by addressing them with honesty, compassion and respect.

Disclosures:
**Pfizer: stockholder*

References:

Antiretroviral Pregnancy Registry Research Park, 1011 Ashes Drive, Wilmington, NC 28405,
Tel: 800.258.4263, Fax: 800.800.1052, www.APRegistry.com
ACOG technical bulletin. Number 205-May 1995. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1995 Aug 50 (2):201-7.
Bershoff-Matcha SJ, Mundy LM, Henry JV. 11th CROI; February 8-11,2004;San Francisco, CA. Abstract 939.
Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Clin Infect Dis. 2001. 32(1):124-9.
Boxwell DE, Styrt BA. 39th ICAAC. San Francisco, CA. September 26-29, 1999. Abstract 1284.
Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
CDC. MMWR. 1995. 44 (No. RR-7):1-15.
Collier AC, Helliwell RJ, Keelan JA, et al. Toxicol Appl Pharmacol. 2003;192:164-73.
Cooper ER, et al. J Acquir Immune Defic Syndr. Hum Retrovirol. 2002. 29(5):484-94.
Corey L, et al. J Acquir Immune Defic Syndr. 2004 Mar 15;35(5):435-445.
Dabis F, et al. 14th IAS. Barcelona, Spain, July 7-12, 2002. Abstract. ThOrD1428.
Dancis J et al. J Acquir Immune Defic Syndr. Hum Retrovirol, 1993. 6(1):2-6.
Dorenbaum A et al. JAMA. 2002. 288(2):189-98.
Dube MP, Sattler FR. AIDS Clinical Care. 1998. 10(6):41-4.
Eastone JA, Decker CF. Ann Intern Med. 1997. 27(10):948.
Fisac et al. Metoabolic changes in patients switching from a protease inhibitor-containing regimen to abacavir, efavirenz, or nevirapine: 24-month results of a randomized study. Abstract 78.
Fiscus SA, et al. Pediatr Infect Dis J. 2002. 21(7):664-8.
Food and Drug Administration. Food and Drug Administration, Public Health Service, Department of Health and Human Services. Rockville, MD: June 11, 1997.
Guay LA, et al. Lancet. 1999. 354(9181):795-802.
Imperiale SM, Stern JO, Love JT, et al. 4th International Workshop on Adverse Events and Lipodystrophy in HIV. San Diego, CA. September 22-25, 2002. Abstract 87.
Johnson KM, Alarcon J, Watts DM, et al. AIDS. 2003 Mar 7;17(4):605-12.
Kuhn L, Stein Z, and Susser M. Paediatric & Perinatal Epidemiology. 2004. 18 (1): 10-16.
Knudtson E, Para M, Boswell H, Fan-Havard P. Obstet Gynecol. 2003. 101(5 Pt 2):1094-7.
Lallemant M, et al. N Engl J Med. 2000. 343(14):982-91.
Lallemant M, et al. 14th International AIDS Conference, Barcelona, Spain. July 7-12, 2002. Abstract. LbOr22.
Langlet P, Guillaume M-P, Devriendt J, et al. Gastroenterol 2000; 118 (suppl 2): Abstract 6623. (101st Annual meeting of the American Gastroenterological Association, San Diego, CA. May 21-24, 2000).
Laurence J., Lessons from the 11th Conference on Retroviruses and Opportunistic Infections. AIDS Reader. 2004;14:151-53.
Luzzati R, Del Bravo P, Di Perri G, et al. Lancet. 1999. 353(9156):901-2.
Lyons F, Hopkins S, McGeary A., et al. 2nd IAS conference on HIV Pathogenesis and Treatment. Paris, France. July 13-16, 2003. (late breaker).
Mandelbrot L, Kermarrec N, Marcollet A, et al. AIDS, 2003. 17(2):272-3.
Mandelbrot L, et al. JAMA, 2001. 285(16):2083-93.
Martinson N, Morris L, Gray G, et al. 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 38.
Mazhude C, Jones S, Murad S, et al. AIDS. 2002. 16(11):1566-8.
Moodley et al. J Infect Dis. 2003. 187(5):725-35.
Murphy R, Katlama C, Weverling GJ, et al. 11th CROI; February 8-11, 2004; San Francisco, CA. Abstract 718.
Petra Study Team. Lancet, 2002. 359(9313):1178-86.
Sandberg JA, et al. Toxicologist. 1994. 14:434.
Sarner L, Fakoya A. Sex Transm Infect. 2002. 78(1):58-9.
Shaffer N, et al. Lancet. 1999. 353(9155):773-80.
Shaffer N, et al. N Engl J Med. 1999. 340(13):1042-3.
Sperling RS, et al. N Engl J Med. 1996. 335(22):1621-9.
Stern JO, Love JT, Robinson PA, et al. 14th International Workshop on Adverse Events and Lipodystrophy in HIV. San Diego, CA. September 22-25, 2002. Abstract LBOr15.
Stiehm ER, et al. J Infect Dis. 1999. 179(3):567.
Tien PC, Cole SR, Williams CM, et al. J Acquir Immune Defic Syndr. 2003;34:461-66.
Visnegarwala F, Krause KL, Musher DM. Ann Intern Med. 1997. 127(10):947.
Wade, et al. N Engl J Med, 1998. 339(20):1409
World Health Organization. WHO Technical Consultation on behalf of the UNFPA/UNICEF/WHO/UNAIDS Inter-Agency Task Team on Mother-to-Child Transmission of HIV. Geneva: World Health Organization, 2001. Report No. WHO/RHR/01.28.

HEPPIGRAM: Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal HIV-1 Transmission

Adapted from the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States, November 26, 2003
http://www.aidsinfo.nih.gov/guidelines/perinatal\PER_112603.html#table3

SCENARIO #1

HIV-infected pregnant women who have not received prior ART

- Pregnant women with HIV infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of ART should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed.
- The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, should be recommended for all pregnant women with HIV-infection regardless of antenatal HIV RNA copy number to reduce the risk for perinatal transmission.
- The combination of ZDV chemoprophylaxis with additional ARVs for treatment of HIV infection is recommended for infected women whose clinical, immunologic or virologic status requires treatment or who have HIV RNA over 1,000 copies/mL regardless of clinical or immunologic status.
- Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.

SCENARIO #2

HIV-infected women receiving ART during the current pregnancy

- HIV-infected women receiving ART for whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible.
- For women receiving ART for whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of ARV administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.
- Regardless of the antepartum ARV regimen, ZDV administration is recommended during the intrapartum period and for the newborn.

SCENARIO #3

HIV-infected women in labor who have had no prior therapy

- Several effective regimens are available. These include:
  1. Intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn;
  2. Oral ZDV and 3TC during labor, followed by one week of oral ZDV/3TC for the newborn;
  3. A single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours*;
  4. The two-dose nevirapine regimen combined with intrapartum intravenous ZDV and six week ZDV for the newborn.
  5. In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

**These recommendations may change due to the high rate of nevirapine resistance. Please refer to the following guidelines for updates: www.cdc.gov/mmwr/preview/mmwrhtml/rr5118a1.htm*

SCENARIO #4

Infants born to mothers who have received no ART during pregnancy or intrapartum

- The six-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn.
- ZDV should be initiated as soon as possible after delivery - preferably within six-12 hours of birth.
- Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs.
- In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4+ count and HIV RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if HIV-infected, treatment can be initiated as soon as possible.

Note: *Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision not to accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.*

Letter from the Editor

Dear Correctional Colleagues:

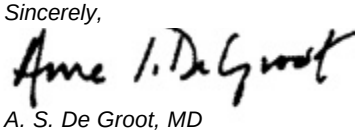
In keeping with HEPP Report tradition, the treatment of HIV-infected women is the focus of our May issue. I'm especially pleased to present Dr. Beth Weaver's report on mother-to-child transmission prevention (MTCP) in this issue. She provides updated guidelines on MTCP, but it's worth noting that these guidelines change rapidly. For example, it is highly likely that treatment of the HIV-infected woman presenting during labor will be modified to short course combination therapy (such as nevirapine and combivir, together, for at least one month following delivery), since single-dose nevirapine has been associated with high rates of resistance due to the long "tail" of detectable drug levels following administration. The best course to follow when confronted with lipodystrophy in an HIV-infected woman is, as yet, uncertain. Dr. Weaver provides a review of the most recent revelations related to this topic, gleaned from the February 2004 CROI conference. And, interestingly enough, this issue of HEPP Report also includes a discussion of contraception and antiretrovirals. Thus we are once again made aware that HIV-infected women are vibrant, sexually active and often still desire to have children.

We need to pause, in this month of that celebrates maternity, to consider the prevalence of HIV infection among pregnant women all over the world. Just a few statistics of note: The prevalence of HIV infection among pregnant women in Bostwana is 32%. In Swaziland, the rate is 40%. In South Africa the rate is 50 %. In Zambia the rate is 69%. These statistics are sobering –and remind us that we should do all that we can to prevent the further transmission of HIV infection to babies, no matter what country we call home.

Of course, neither sex nor pregnancy are events meant to occur during incarceration. We therefore bring you these updates so that you can better plan your care of women patients as they are being released back to the community. The fact is, your patients often resume their lives where they left off (without restarting illicit drug use, we hope). I always tell my soon-to-be-released patients to have more than one plan - Plan A and Plan B. Even though they may not be planning to get pregnant, I have a discussion with them about how best to manage their pregnancy, should it occur. The good news that all of our patients deserve to hear is that HIV transmission to the newborn does not have to happen. Therefore, as you are planning ahead for your Mother's Day celebrations, (May 9th this year, in case you were wondering!) do give some thought to future generations of children who will thank you for teaching your patients about Plan B.

As always, we thank our readership for their interest in HEPP Report and we welcome your comments.

Sincerely,



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HIV 101: Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

Antiretroviral drug	FDA pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Not completed	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30-0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose)
Zidovudine (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent-near lethal dose)
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodent-ventricular septal defect)
Efavirenz (Sustiva)	C	Yes (cynomologus monkey, rat, rabbit)[~1.0]	Positive (increased hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)	Positive (cynomologus monkey-anencephaly, anophthalmia, microophthalmia)
Nevirapine (Viramune)	C	Yes (human)[~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	Not Completed	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (increased benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/ Ritonavir (Kaletra)	C	Unknown	Not Completed	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Nelfinavir (Viracept)	B	Minimal (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (rodent, liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Not completed	Negative
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not Done	Negative

FDA pregnancy categories:
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 reproductive studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant 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.*

SPOTLIGHT: HIV Management in a Malian Women's Prison

Julia Noguchi, Managing Editor, HEPP Report*

Mali continues to rank among the few sub-Saharan African countries with a low prevalence of HIV/AIDS in the general population. UNAIDS estimated at yearend 2001 that 110,000 adults and children in Mali were living with HIV/AIDS, with an adult prevalence of 1.7 percent–comparable to that of the US. Yet a suspected higher prevalence in "bridge" populations, such as long-distance truck drivers, ambulatory vendors, and female sex workers portends a wider epidemic. UNAIDS also estimates that 55 percent of adults living with HIV/AIDS in Mali are women.

The Bollé Correctional and Rehabilitation Facility for Women and Girls, (Centre Spécialisé de Détention de Rééducation et de Réinsértion pour Femmes et Filles Mineurs de Bollé), which lies on the outskirts of the capitol city of Bamako, Mali, is one of seven prisons in the nation. Bollé, the largest facility for female inmates in the country, opened its doors in 1998, and houses from 50 to 70 women and girls at a time. Malians make up the majority of the detainees; however, nearly all West African countries are represented.

Apart from the lack of resources and medical care, the Bollé facility greatly differs from its US counterparts in that the inmates are entirely self-sufficient. In the past, non-governmental organizations were able to support the prison with donations of food and medical supplies, but prison director Diarra Assétou Kouyaté said that these organizations could no longer afford to provide assistance. Trades such as cloth-dying, sewing, and soapmaking not only afford these women with skills to survive once they are released, but also function as a means of economic support for the facility. Children of the inmates are permitted to live at the prison until the age of four, and are completely in their mother's charge since the prison cannot afford to feed, clothe, or provide medicines for them.

Relative to the US, there are very few women imprisoned in Mali. Kouyaté, who toured prisons in the US several years ago, explained that "in Mali the women are well-behaved." While the Bollé prison is recognized as being one of the best correctional facilities in West Africa for preserving the dignity of inmates, Kouyaté stated bluntly that "this is no hotel." Surprisingly, most of the women are not incarcerated for prostitution or drug-related charges. They are serving sentences for infanticide. The influx of young women to urban areas is fueled by a desire to earn a better living and find a husband. Many of them, however, end up involved in prostitution. Faced with an unwanted pregnancy or lack of financial means to provide for the baby, the woman may resort to "the worst of crimes," said Kouyaté. The other small percentage of crimes for which the women are convicted include involuntary homicide, fraud, and having abandoned their families.

HIV Testing

Routine HIV testing does not exist in the women's prison. Occasionally, HIV tests are performed when a woman is chronically ill, or goes to the hospital to have a child or undergo surgery. Accordingly, HIV prevalence is unknown. As in Malian society, AIDS remains a taboo subject in the correctional environment. "Because of the stigma associated with AIDS in Mali, the women here simply do not believe the facts about AIDS," said Kouyaté. Not surprisingly, most incarcerated women here would likely refuse to be tested even if given the opportunity. The administration has always made concerted efforts to keep testing as discreet as possible but personal information travels fast inside the prison walls. "These women are very perceptive," Kouyaté said. "They know what goes on here better than the staff does." The Bollé prison does not have recourse to legislation on informed consent or any laws regarding HIV testing in the correctional setting. Upon further investigation of what is an extremely delicate–but not a litigious–issue in Malian corrections, Kouyaté acknowledged the need for protocols for a confidential and effective testing system.

Compassionate Release

As a general rule, prisoners who are confirmed to be HIV-infected are sent to appear before a district judge and are routinely granted compassionate release. "We simply don't have the means to provide care and treatment for them…These women are not left to die in prison," said Kouyaté. Antibiotics for treatment of OIs are sorely needed. Not only are antiretrovirals (ARVs) not available on the inside, but the medical staff is also not trained in pre- or post-test counseling. By the time a case of HIV is suspected by the medical staff, the woman has usually progressed to full-blown AIDS. Since 1999, there have been six women who have tested positive for HIV at Bollé, five of whom died of AIDS following compassionate release. The sixth woman, who has not developed full-blown AIDS, is being treated with ARVs and followed by CESAC (Centre de Soins, d'Animation et de Conseil), a Malian governmental organization that provides HIV/AIDS prevention, treatment and counseling. Created in 1996, one of the organization's primary objectives is the prevention of mother-to-child transmission of the virus. Following release by the judge, a prisoner who tests positive for HIV is referred to this center for treatment and follow-up.

Access

Supply, distribution and cost constitute the triumvirate of challenges in the fight against the AIDS pandemic in Africa. Currently, the following ARVs are approved for treatment of HIV infection in Mali: didanoside, zidovudine, lamivudine, stavudine, nevirapine, efavirenz, nelfinavir and indinavir. There are not enough of these medications, however, to keep them in stock at the pharmacy, which renders treatment interruption inevitable. An infrastructure for dispensing these drugs does not exist, nor does the personnel for distributing them. Furthermore, difficulties in accessing transportation to and from the hospital or clinic for treatment and proper follow-up are realities in Mali.

Cost reduction of ARVs–the issue that seems to be dominating recent discourse on AIDS in the developing world–is a key factor for making treatment more accessible to the population. IMAARV (Initiative Malienne d'Accès aux Antirétroviraux) is a program financed by the state and private sector whereby eligible individuals can receive ARVs and medications for opportunistic infections at reduced cost since they come from bulk suppliers. Although IMAARV has committed to instituting two-year treatment programs that aim to improve the quantity and quality of available ART, cost remains a formidable barrier. For example, 50 percent cost reduction in ARVs translates into about 45,000 CFA/month (about $88 (US)). Yet, given that the cost is higher than the average monthly household income, ARVs are still inaccessible to 90 percent of the HIV-infected population of Mali.

Conclusion

Today, the AIDS situation in Mali is not as dire as it is in some African nations. However, significant seasonal migration of agricultural workers to Senegal, Côte d'Ivoire, (which has the highest HIV prevalence in West Africa), and France during Mali's off-agricultural season could have a serious effect on the spread of HIV in Mali in years to come. The past decade bears witness to the fact that no country is insulated from the risk of the epidemic. The Bollé prison has many stories to tell about the women for whom release into the free world has equated further confinement by AIDS. The prison medical staff shared only a handful of these inmates' stories, each one unique but with the same tragic ending. The hope is that one day these young women will re-enter the free world as healthier and more confident individuals; this can be accomplished with the help of governments, NGOs, and individuals committing to care more–and to care sooner.

Disclosures: **Nothing to disclose.*

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Register online at: http://www.aids2004.org/

Inside News

Valacyclovir Prevents Transmission of HSV
HSV (Herpes Simplex Virus) is the leading cause of genital ulcers in both developed and developing countries. According to a recent study on valacyclovir given once daily to a patient with genital herpes, valacyclovir significantly reduces the rate of HSV transmission. This study involved a prospective, randomized, placebo-controlled trial of valacyclovir (500 mg/day for 8 months) in 1,484 immunocompetent, heterosexual, monogamous couples that were discordant for herpes simplex virus-2 (HSV-2) symptomatic genital infection. A subset analysis was done in 89 patients to determine the effect of valacyclovir on viral shedding using HSV polymerase chain reaction (PCR) analysis of genital swab specimens. As demonstrated in the study, viral shedding is notably reduced in the source patient. The potential application of this information is important for couples that are discordant for HSV. However, this may have an even more important application for reducing transmission of HIV infection, as these ulcers have high concentrations of HIV in co-infected patients.
Corey L, Wald A, Patel R, et al. NEJM. 2004;350:11-20

FDA Approves First Oral Fluid Based Rapid HIV Test Kit
The FDA has approved the use of oral fluid samples with a rapid HIV diagnostic test kit that provides screening results with over 99 percent accuracy in as little as 20 minutes. Until now, all rapid HIV tests required the use of blood in order to get such rapid results. In addition to simplifying the testing process and precluding the need for a blood sample, use of the oral collection component reduces risk to healthcare workers performing the test by reducing exposure to blood and sharps. The Centers for Disease Control and Prevention (CDC) has estimated that one fourth of the approximately 900,000 HIV-infected people in the US are not aware that they are infected.
NATAP - www.natap.org, March 26, 2004

HAART Treatment During Acute HIV-Infection Not Recommended
A recent joint study from Australia and the US concluded that antiretroviral treatment of primary HIV infection (PHI) may not be clinically justified on the basis of current evidence. Where does this leave the clinician who has identified a patient as acutely infected with HIV? In some regards, the question of when to treat in PHI is similar to those patients identified with established infection; however, at the start of the disease course there is the possibility of proportionally larger benefits, making this an important question to answer. Based on the currently published data, there is no clear evidence that patients with access to ART have any greater clinical benefit if therapy is introduced immediately during or prior to their seroconversion illness, nor are there comparative data to suggest that short-term use of HAART during PHI can alter future disease progression. Currently, no evidence from these studies suggests that therapy during PHI results in a reduction in clinical progression compared with use of effective therapy in later disease.
Smith, Don E. et al. AIDS: Volume 18(5) 26 March 2004 pp 709-718.

Study: Detecting Human Papillomavirus DNA in Men
A study presented at the Human Papillomavirus 2002 International Conference in Paris evaluated methods for detection of genital human papillomavirus (HPV) DNA in men. In this study, samples were obtained from three consecutive groups of 10 men attending a sexually transmitted disease clinic by use of (1) a saline-wetted Dacron swab alone, (2) a saline-wetted cytobrush, or (3) emery paper (600A-grit Wetordry Tri-M-ite; 3M) abrasion followed by a saline-wetted Dacron swab. By use of a polymerase chain reaction-based assay, 45% of emery-paper samples were found to be positive for -globin, compared with 23% of swab-alone and 0% of cytobrush samples. Subsequently, emery paper and saline-wetted Dacron swabs were used to obtain penile shaft, glans, foreskin, and scrotum samples from 318 male university students. Urine samples were also obtained. Of 1323 samples tested, 1288 (97%) were found to be positive for -globin. HPV DNA was detected in samples from 104 men (33%): 24% from the penile shaft, 16% from the glans, 28% from the foreskin, 17% from the scrotum, and 6% in urine. The HPV prevalence was similar for circumcised and uncircumcised men. Testing multiple sites increased the number of men for whom HPV DNA was detected.
Bethany A. Weaver et al. Evaluation of Genital Sites and Sampling Techniques for Detection of Human Papillomavirus DNA in Men. JID 2004;189:677-685.

Resources

HIV InSite Knowledge Base, University of San Francisco
http://hivinsite.ucsf.edu

AIDS Alliance for Children, Youth & Families
www.aidsalliance.org/aids_alliance/index.html

The National Commission on Correctional Health Care
www.ncchc.org/

Women, Children, and HIV
http://womenchildrenhiv.org/

Albany Medical Center's AIDS Program
www.amc.edu/patient/hiv/hiv_correctional.htm

US Dept. of Health and Human Services: Services to People with HIV in Correctional Settings
http://hab.hrsa.gov/special/corrections_index.htm

Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for 1 hour in category 1 credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through November 30, 2004. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. A 25 year-old pregnant women with HIV received intrapartum prophylaxis therapy during the first trimester but then discontinued therapy after 12 weeks of gestation. It is recommended that she:
   a) start an entirely new regimen
   b) resume her old regimen, reintroducing one drug at a time
   c) reintroduce all drugs simultaneously
   d) stop all drugs and receive a single dose of nevirapine at the onset of labor

2. An initial evaluation of an HIV-infected pregnant woman should include an evaluation of:
   a) CD4 cell count
   b) history of prior or current ART
   c) level of plasma RNA
   d) gestational age
   e) supportive care needs
   f) options for ART based on the history of previous treatment
   g) all of the above

3. Protease inhibitors that have a drug-drug interaction with oral contraceptives include:
   a) indinavir and nelfinavir
   b) amprenavir and ritonavir
   c) atazanavir and ritonavir
   d) amprenavir and indinavir

4. For HIV-infected women in labor who have had no prior antiretroviral therapy, possible regimens may include:
   a) oral ZDV and 3TC during labor, followed by one week of oral ZDV/3TC for the newborn
   b) a single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours
   c) a only
   d) a and b
   e) none of the above

5. Studies have shown that hepatic toxicity with systemic symptoms due to nevirapine were more than three times more common in women than in men. True or False.
   a) True
   b) False

6. According to a recent study, the percentage of nevirapine-resistant virus that occurred in mothers was:
   a) less than one-third
   b) greater than one-third
   c) one-half
   d) greater than half

HEPP Report Evaluation

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3. What future topics should HEPP Report address?

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