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Repeat Pregnancies Among HIV-Infected Women Enrolled in Clinical Trial PACTG1022

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To the Editors:

Since the great majority of HIV-1-infected women worldwide are of reproductive age, both intended and unintended pregnancies occur relatively frequently in this population[1,2] and may be increasing in the context of highly active antiretroviral therapy compared to earlier eras.[1, 3] Many HIV-1-infected women desire childbearing.[4] However, unintended pregnancies may result in inadvertent exposure of the developing fetus to potentially teratogenic drugs such as efavirenz, or to newer medications of unknown risk. Prevention of unintended pregnancy among HIV-1-infected women is a high priority.

We evaluated the rate and potential predictors of repeat pregnancy during two years of postpartum follow-up among women enrolled to a clinical trial that compared two initial antiretroviral regimens in pregnancy. These women had intensive follow up during and after pregnancy, including extensive contraceptive counseling, and were specifically counseled to avoid subsequent pregnancies on study. We hypothesized that occurrence of repeat pregnancies might be predicted by specific demographic and/or clinical characteristics. By identifying these characteristics, we hoped to target HIV-infected women most at risk for repeat pregnancy with more focused contraceptive counseling.

Details of study funding and participants appear online at XXXXX.

PACTG 1022 Participants

The following individuals assisted with conducting PACTG 1022: Ana Melendrez, RN, Michael Neely, MD, and James Homans, MD, University of Southern California, Los Angeles; Jennifer Griffin, RN, Deborah Hattenback, RN, and Sylvia Muniz, State University of New York, Stony Brook; Dawn Barnes, RN, and Anita Whitten, RN, Columbus Regional Healthcare System; Robert Pass, MD, and Terry Byars, MD, University of Alabama; Chivon D. Jackson, RN, Christine M. Owen, RN, and Valencia Y. Johnson, RN, Baylor College of Medicine; Alice Higgins, RN, and Philip LaRussa, MD, Columbia University; Midnela Acevedo, MD, Elvia Pérez-Hernández, MPH, and Antonio Rodriguez-Mimoso, MD, City Hospital at San Juan; Nina Sublette, RN, Pat Flynn, MD, Jill Utech, RN, and Mary Dillard, RN, University of Tennessee Health Science Center; Deborah Goldman, ARNP, Michele Acker, ARNP, and Kathey Mohan, ARNP, University of Washington; Joseph Mrus, MD, Patricia Kohler, RN, and Michelle Saemann, RN, University of Cincinnati; Margaret A. Keller, MD, Marie Beall, MD, and Judy Hayes, RN, University of California, Los Angeles; Kathy Kabot, Paula Karnick, Gloria Seals, and Charles Lampley, Mount Sinai Hospital; Andrew D. Hull, MD, Patricia Franklin, FNP, Mary Caffery, RN, and Stephen A. Spector, MD, University of California, San Diego; Patricia Strock, PA, Jhoanna Roa, MD, Patricia Houston-Yu, MS, and Sohail Rana, MD, Howard University; Saroj Bakshi, MD, Murli Purswani, MD, Marilyn Crane, CNM, and Mavis Dummitt, RN, Bronx-Lebanon Hospital.

Pediatric AIDS Clinical Trials Group protocol 1022 (P1022) was a randomized, open label study to determine the better antiretroviral strategy (protease inhibitor (PI) -including versus PI-sparing) for HIV-infected pregnant women initiating antiretroviral therapy during pregnancy. Women initiated assigned therapy between 10 and 30 weeks of gestation and were followed through two years after delivery. More details have been published.[5] Enrollment was terminated early because of greater than expected toxicity in the nevirapine arm,[5] but enrolled women continued study follow-up.

After delivery, women were seen for visits at 2, 8, 16, 24, 32, 40, 48, 56, 72, 88, and 104 weeks. At each visit except the two week visit, a urine pregnancy test was completed. Women received contraceptive counseling during pregnancy and at each postpartum visit. Current contraceptive use was queried at each visit after delivery. Condom use was reinforced, and women were provided with additional methods or referred for contraceptive services if necessary. If a subsequent pregnancy was diagnosed, study medications were discontinued until a pregnancy outcome occurred. Women were followed on study and received antiretrovirals in from their prenatal care provider.

We assessed the number of subsequent pregnancies per 100 person-years using the exact binomial method.[6] Characteristics of women with or without a subsequent pregnancy were compared using t-tests for normally distributed continuous variables, Mann-Whitney for non-normally distributed continuous variables, and chi square or Fisher's exact test for categorical data.

Thirty-nine women were enrolled, 21 randomized to nelfinavir and 18 to nevirapine, both with zidovudine and lamivudine. One subject withdrew before treatment was dispensed and one woman died in the early postpartum period of fulminant hepatic failure, leaving 37 women eligible for postpartum follow-up. Eleven subsequent pregnancies occurred among nine women during follow up for a pregnancy rate of 16.5/100 woman years of follow up (95% CI: 8.5%–27.5%). Censoring women at the first subsequent pregnancy, the rate was 15.3/100 woman years (95% CI: 7.2%, 26.9%). Outcomes of the subsequent pregnancies included three spontaneous abortions, two induced abortions, three live births, and three ongoing pregnancies, two in the third trimester and one in the early second trimester.

There were no significant differences in demographic characteristics, pregnancy history, smoking, drug or alcohol use, CD4+ lymphocyte count, HIV RNA level, or treatment arm between women with or without a subsequent pregnancy. However, women with subsequent pregnancies were significantly less likely to use a second contraceptive method in addition to male condoms. Of the 35 women with complete contraception information, only one of 8 women in the group with repeat pregnancies used a hormonal method of contraception in the postpartum period compared to 21 of 27 women without repeat pregnancies who used an additional method (p=0.002, Fisher's exact test). Eight women (22%) underwent sterilization and 13 (35%) chose oral contraceptives or depot medroxyprogesterone during the postpartum period in addition to condoms. Excluding the 8 women who chose to be sterilized postpartum, the subsequent pregnancies occurring among nine women during follow up gave a pregnancy rate of 21.4/100 woman years of follow up (95% CI: 11.3%–35.3%). Censoring women at the first subsequent pregnancy, the rate was 20.8/100 woman years (95% CI: 10.0%, 36.0%).

The pregnancy rate among HIV-infected women in this study of 15–21/100 person-years is generally higher than that reported for similar HIV-infected women in the US and Europe. In a report from the Womens' Interagency HIV Study (WIHS), an ongoing cohort of women in the US, the pregnancy rate among HIV-infected women was 7.4/100 person-years compared to 15.2/100 person-years among similar HIV-uninfected women.[1] The pregnancy rate was stable over time among HIV-infected women but the rate of induced abortion decreased in the

HAART era.[1] A study of women with known seroconversion date in Europe compared the pregnancy rate before and after the diagnosis of HIV infection and found the rate of pregnancy decreased from 8.6/100 person-years before HIV diagnosis to 8.2 in the first four years after diagnosis and 6.0 after four years.[2] The proportion of induced abortions increased significantly after HIV diagnosis ($p < 0.05$), although the majority of the follow up period was in the pre-HAART or early HAART era. The pregnancy rate in the Adult/Adolescent Spectrum of HIV Disease Project (AASHDP) among 8857 women was 5.5/100 person-years with an increased rate during 1997–2001 compared to earlier periods (relative risk 1.2, 95% confidence intervals 1.1–1.4).[3] Women enrolled to the current study were all receiving HAART, which may have influenced the pregnancy rate because of improved maternal health and decreased rate of transmission, but rates were still higher than recent rates in WIHS or the AASHDP. Rates in the current study are more similar to those reported among HIV-infected adolescents, as for example in the Reaching for Excellence in Adolescent Care and Health (REACH), where the rate among HIV-infected adolescents was 20.6/100 person-years.[7] However, only six (16%) of the women in the current study were under age 20.

The relatively high pregnancy rates in P1022 compared to WIHS and AASHDP were seen despite the fact that the women were enrolled during pregnancy, were specifically advised to avoid recurrent pregnancy because of potential teratogenic risk, and received ongoing contraceptive counseling and obstetrical and gynecologic care facilitated through the study. Women who conceived during follow up were more likely to be using condoms alone for contraception, underscoring the need for dual method use for enhanced contraceptive efficacy. While pregnancy rates with perfect condom use are estimated at 2% per year, rates with typical use are thought to be closer to 15%/year.[8] Many of the women reported condom use less than 100% of the time with sexual activity. The reasons for lack of uptake of dual method use for women enrolled to this study were not explored, but would be important to understand to enhance dual method use in the future.

One potential reason for lack of dual method use may be provider or patient concerns regarding the interactions of HIV infection or antiretroviral therapy and contraceptive methods. Indeed both nelfinavir and nevirapine have been shown to decrease levels of ethinyl estradiol from oral contraceptives, and nelfinavir has been shown to lower norethindrone levels, which may affect contraceptive efficacy.[9] It is unclear whether drug interactions contributed to the pregnancy that occurred in the one woman on oral contraceptives in the study. Depot medroxyprogesterone (DMPA) did not demonstrate clinically significant pharmacokinetic interactions with nelfinavir, efavirenz, or nevirapine, but data are limited regarding interactions of other antiretrovirals with DMPA.[10] Further study of potential interactions between hormonal contraceptive formulations and antiretroviral agents is needed to be able to provide appropriate counseling to HIV-infected women on antiretrovirals.

An additional concern is the potential effect of pharmacologic doses of reproductive hormones in contraceptives on HIV disease progression. A recent randomized trial, initially designed to compare contraceptive efficacy and patient acceptance of the intrauterine device (IUD) to hormonal contraceptives among HIV-infected women, found an increased risk of HIV disease progression among women using hormonal contraception (HR 1.7, 95% confidence interval 1.1–2.5).[11] Further study is required to assess this effect and to evaluate whether differences in HIV progression are seen by contraceptive method among women on antiretroviral therapy. This study and a previous study from Kenya have both demonstrated the safety of the IUD as a contraceptive option for selected HIV-infected women desiring a method in addition to condoms, despite initial concerns regarding the potential for increased risk of pelvic infections among HIV-infected women.[11,12] Pending further data, both IUD's and hormonal contraceptives may be offered to appropriately screened HIV-infected women who desire added contraceptive efficacy.

The repeat pregnancy rate among women enrolled to P1022, a study of optimal therapy during and after pregnancy, was higher than expected based on previous studies.[1,3] The only risk factor identified for a repeat pregnancy was use of male condoms as the sole contraceptive agent. Women should be counseled regarding appropriate condom use, and offered additional methods of contraception, if pregnancy is not desired. In addition, prevention of unintended pregnancies in HIV-infected women will reduce the number of HIV-infected infants.[13] Concerns regarding interactions of hormonal contraceptives with antiretrovirals and HIV disease progression point to an increasing role for IUD's and female barrier methods such as the diaphragm and cervical cap among HIV infected women and underscore the need for additional research in this area.

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