

## Long-Term Pill Use, High Parity Raise Cervical Cancer Risk Among Women with Human Papillomavirus Infection

Use of oral contraceptives for five years or more appears to raise the risk of cervical cancer among women infected with human papillomavirus (HPV). The odds of developing cervical cancer are nearly tripled among women who use the pill for 5–9 years and quadrupled among those who rely on the pill for 10 years or more, compared with the odds among never-users.<sup>1</sup> An HPV-positive woman's likelihood of developing cervical cancer is also associated with the number of times she has given birth. Compared with those who have never borne a child, HPV-infected women who have had 1–2 births have twice the odds of developing cervical cancer, and those who have given birth seven or more times have four times the odds.<sup>2</sup>

Oral contraceptive use and high parity long have been thought to be tied to the development of cervical cancer, yet past research into these associations has been hindered by a lack of information about whether women were infected with HPV, one of the main immediate causes of cervical cancer. A series of studies by the International Agency for Research on Cancer (IARC) included assessments of women's HPV status and thus provide an opportunity to investigate the independent role of reproductive factors in the development of cervical cancer.

### Data and Analyses

IARC sponsored case-control studies of invasive cervical cancer between 1985 and 1997 in eight countries (Brazil, Colombia, Morocco, Paraguay, Peru, the Philippines, Spain and Thailand). In addition, in two countries (Colombia and Spain), research was conducted on the occurrence of carcinoma in situ. All of the studies followed similar protocols. Cases (women with cervical cancer) and controls (women recruited either from the same hospital or from the same region as the cases) were interviewed in person. Interviewers collected detailed information on participants' background characteristics, sexual and reproductive behavior, contraceptive history, smoking habits, history of sexually transmitted diseases, Pap smear history and hygienic practices. HPV infection was diagnosed through analysis of

cervical cells collected from participants.

Data from these studies were pooled, yielding a total of 1,853 women with cervical carcinoma (either invasive or in situ) and 1,916 controls. HPV was detected in tissue samples from 1,676 cases and 255 controls; all subsequent analyses were focused on these women. The investigators used logistic regression to control for the effects of study center, age, education, smoking, lifetime number of sexual partners, age at first intercourse, Pap smear history, and pill use or parity (depending on the factor being studied).

### Pill Use and Cervical Cancer

Roughly one-third of both cases and controls who were HPV-positive had ever used oral contraceptives; the average duration of use was 6.1 years. The data suggest that ever-users of oral contraceptives were slightly more likely than never-users to have developed cervical carcinoma (odds ratio, 1.4), although this increase was not statistically significant.

Among women who had used oral contraceptives for no more than four years, the odds of cervical cancer were no different from those among never-users. However, women who had taken the pill for 5–9 years had a significantly elevated risk of cervical cancer (odds ratio, 2.8), and those who had done so for 10 or more years had even further increased odds (4.0).

Compared with never-users, women who began taking oral contraceptives before age 20 or in their early 20s had elevated odds of cervical neoplasia (odds ratios, 2.9 and 1.7, respectively), while those who did so later had no increased risk. When the investigators examined duration of use and age at first use together, they found that women who had used the pill for five or more years were at similarly elevated risk regardless of whether they began using oral contraceptives before or after age 25. This finding leads them to comment that cancer risk is “more likely to be determined by duration of oral contraceptive use than by age at first use.”

Current pill users and women who had used the pill in the preceding 1–5 years had increased

risks of cervical carcinoma (odds ratios, 2.6 and 4.7, respectively), but use in the more distant past was not associated with the risk of disease. The effect of recency of use, however, depended on duration of use. For women who had used the pill for less than five years, the only effect was a marginal increase in risk among those who had used it within the previous five years. By contrast, longer-term users had an elevated risk of cancer that persisted for up to 14 years after they discontinued use.

### Parity and Cervical Cancer

More than nine in 10 women with cancer and controls had given birth. Regardless of their cancer status, study participants had had about five births each, and the median age at first birth was 20–21 years. Cervical cancer risk rose steadily as a woman's number of births increased. Compared with nulliparous women, those who had borne one or two children had 1.8 times the odds of developing cancer; odds ratios were 2.6–2.8 for those who had had 3–6 births and 3.8 for those with seven or more births. Likewise, cervical cancer risk was closely linked to age at first birth; the odds ratio was highest among women who gave birth at age 16 or younger (4.4), and then ranged from 2.5 among those who initially delivered at ages 17–19 to about 2.2 among those who did so at age 20 or older.

Type of delivery also appears related to cervical cancer: The few women who had given birth only by cesarean section had a risk of cervical cancer no different from that among women with no lifetime births. However, the odds of cervical neoplasia were elevated among women who had delivered only vaginally (2.6) or both vaginally and via cesarean section (2.2). In contrast, the only association seen between a history of abortion (either induced or spontaneous) and cervical cancer was a significantly reduced likelihood of cancer among women who had had two or more abortions (odds ratio, 0.6).

When the researchers restricted their analysis to women with at least one birth and controlled for the effects of age at first full-term preg-

nancy, the overall number of full-term pregnancies still predicted cervical cancer risk: Compared with women who had had 1–2 births, those who had borne three or four children had 1.5 times the odds of disease; the odds ratio climbed to 2.3 among women with seven or more lifetime births. This relationship was more pronounced among women whose cancer was diagnosed before age 45 than among those who found out later that they had cancer.

Women whose first full-term pregnancy occurred 5–14 years previously had elevated odds of cervical cancer (1.7), while those who had first given birth 15 or more years before had no increase in their cancer odds. By contrast, in analyses controlling for the effects of number of full-term pregnancies, age at first full-term pregnancy was no longer associated with cervical cancer risk.

Finally, the investigators examined the combined effects of parity and oral contraceptive use; for all comparisons, nulliparous women who had never used the pill were the reference group. Regardless of women's history of pill use, increasing parity was associated with increased cancer risk. For never-users of oral contraceptives, odds ratios rose from 1.8 for those who had had 1–2 births to 3.4 among those who had borne five or more children. Results were similar for women who had used the pill for less than five years, with odds ratios increasing from 1.9 to 2.6. Among those who had taken oral contraceptives for longer durations, however, the differentials were much sharper; the odds ratio was 4.9 for those with 1–2 lifetime births, 6.0 for those with 3–4 births and 11.8 for those who had given birth five or more times.

### Conclusions

The researchers who analyzed pill use and cervical carcinoma comment that the relationship they found between the two suggests that oral contraceptives promote “some step in the process of HPV-related cervical carcinogenesis.” However, they find no evidence that pill use promotes HPV infection: An examination of all controls in the pooled data showed no association between oral contraceptive use and HPV infection.

As for the findings on parity and cervical cancer, the researchers responsible for those analyses observe that the lack of association between abortion and cancer “provides some hint that events related to the second and third trimesters of pregnancy or to delivery might be relevant” to cervical cancer development. They cite changes in hormonal levels late in

pregnancy that might increase the likelihood of cervical carcinoma.

The author of a commentary published along with the studies observes that they had several shortcomings, including wide confidence intervals in some of the analyses and reliance on just one assessment of HPV status (making it difficult to know how recently infection had occurred). Nevertheless, he notes that the most important aspect of the studies is that because they were restricted to women infected with HPV, they suggest that observed associations between cervical cancer and parity or pill use are not related to differences in levels of HPV infection. Confirmation of these results, the author argues, will bring about “wider acceptance that high parity and long-term use of oral contraceptives can act as cofactors in the genesis of cervical cancer.”<sup>3</sup>—*M. Klitsch*

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## Female Condom Use Rises If Women Receive Good Instruction and Training

Women who receive instruction in female condom use, along with opportunities to practice method-related skills on a pelvic model, have an increased likelihood of using the method, of using it correctly and of viewing it in a favorable light.<sup>1</sup> The strongest predictors of female condom use found in a U.S. trial of an intervention aimed at reducing women's risk of HIV and other sexually transmitted diseases (STDs) were having had instruction and skills training, and intending to use the method.

The trial was conducted between May 1995 and August 1997 in Baltimore, Maryland; New York City; and Seattle, Washington. Women were recruited at community-based programs, family planning clinics and STD clinics, as well as through advertisements, flyers and community presentations. To be eligible, women had to be HIV-negative and at least 17 years old, and they had to have had intercourse with a male partner during the past three months. In

addition, during the past year, eligible women had to have received an STD diagnosis, had three or more sexual partners, or had sex with a man who engaged in risky behavior. A total of 604 women were enrolled and were randomly assigned to a six-week intervention or a control group.

Those assigned to the intervention attended six weekly group sessions in which they were given skills training in communication, goal setting and male condom use; received information and watched a video about the female condom; observed a demonstration of female condom insertion using a pelvic model; and were provided an opportunity to practice on the model. Clinicians encouraged participants to practice inserting the female condom before using it with a partner. Women in the control group attended a one-hour nutrition counseling session and received printed instructions on how to use male and female condoms. Free female condoms were available to all women interested in trying the method.

At study entry and three months after the intervention, the women completed interviews that addressed a range of attitudes toward the female condom. Researchers also asked the women to demonstrate proper female condom use on a pelvic model and rated their skills in using the method. The analyses are based on 442 women who participated in the three-month follow-up.

Overall, the women were predominantly black (58%) or Hispanic (18%) and never-married (73%); their average age was 28.5 years. Roughly eight in 10 were unemployed; only one-quarter had more than a high school education. Four in 10 had at least one dependent child.

At baseline, experience with and attitudes toward the female condom were essentially the same among women assigned to the intervention and those assigned to the control group: Nine percent of each group had ever used a female condom either with a partner or for practice, and 7% had used one with a partner; use in the previous three months was negligible. Asked to rate the female condom on a variety of characteristics, with possible responses ranging from one (poor) to four (very good), women in both groups gave it an average score of 1.3–1.5 at baseline. On average, they performed only 2.7–3.0 out of six method-related skills correctly. About one-quarter of women in each group disagreed that their partner would find the female condom acceptable, fewer than half agreed and the rest did not know.

Three months after the intervention, however, the groups differed sharply on all of these measures. Significantly higher proportions of those in the intervention group than of controls had ever used a female condom (60% vs. 22%) and had used one with a partner (36% vs. 12%). Among those who had used female condoms in the past three months, women who had received instruction had used an average of 1.5, whereas those in the control group had used 0.5. The intervention group gave the female condom a more positive average rating than the control group (3.2 vs. 2.1) and correctly performed a greater number of method-related skills (4.6 vs. 3.3).

In initial comparisons, a number of attitudes, skills and behaviors related to female and male condom use distinguished women who had ever used the female condom (regardless of whether they were in the intervention or control group) from those who had never done so. To determine which factors independently affected use, the investigators conducted logistic regression analyses, controlling for baseline and follow-up differences between ever-users and never-users.

Results of these calculations indicated that participation in the intervention was the strongest predictor of use (odds ratio, 5.5), followed by a stated intention at follow-up to use the female condom (4.5). Other factors associated with increased odds of use were having asked a partner to use a condom in the past 30 days (2.3), feeling confident at follow-up in one's ability to ask a partner to use a condom (1.9) and having had favorable attitudes toward the female condom at baseline (1.2). Women who reported having only casual partners at follow-up were significantly less likely than those who reported having a main partner (exclusively or in addition to casual partners) to use the female condom (0.2).

Noting the importance of factors related to negotiating male condom use in predicting female condom use, the researchers comment that while the female condom "is not strictly 'female-controlled,' ...it may give women more control than the male condom." However, they add, it might not be an option for women who lack negotiation skills. Of paramount importance, they conclude, is counseling that offers both information and a chance for women to practice using the method.—*D. Hollander*

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## Use of Multiple Anti-HIV Drugs Does Not Raise Risk Of Adverse Birth Outcomes

Among HIV-infected pregnant women, those who receive combination antiretroviral drug therapy have rates of premature delivery and stillbirth similar to those receiving monotherapy or no therapy, and they are no more likely to deliver a baby with low birth weight or low Apgar scores, according to a combined analysis of multiple studies performed in the United States.<sup>1</sup> Furthermore, women who take protease inhibitors as part of their combined drug regimen are no more likely to have a premature or very premature delivery or a low-birth-weight infant than are women who use combination therapy without these drugs, monotherapy or no therapy. Among women receiving combination therapy, however, users of protease inhibitors may be more likely than nonusers to have a very low birth weight infant (odds ratio, 3.6).

HIV-infected pregnant women can take antiretroviral drugs to improve their health and decrease the likelihood of mother-to-child HIV transmission, but the impact of these drugs on pregnancy outcomes has not been determined. To examine the effects of antiretroviral treatment on the risks of adverse outcomes, researchers analyzed data from seven clinical studies of HIV-1-positive pregnant women who delivered their infants from 1990 through 1998. The researchers studied the women's characteristics and type of antiretroviral therapy used, as well as the following outcomes for singleton births: premature or very premature delivery (at less than 37 or 32 weeks' gestation, respectively), low or very low birth weight (less than 2,500 g or 1,500 g, respectively), possibly or definitely abnormal Apgar scores (less than seven or four, respectively) at one minute and five minutes, and stillbirth.

Of the 3,266 women identified, 1,590 had received zidovudine monotherapy, 533 had received a combination of antiretroviral drugs (396 whose treatment included protease inhibitors and 137 whose treatment did not) and 1,143 had not received any antiretroviral drugs. Compared with women who had received monotherapy, those who had received any combination therapy were generally older (median age, 28 vs. 27), had lower median CD4+ cell counts (286 vs. 358 per cubic millimeter) and were less likely to have used illicit drugs during pregnancy (16% vs. 25%). Women who

had received antiretroviral treatment had lower median CD4+ cell counts than did untreated women (343 vs. 450 per cubic millimeter) and were also less likely to have used tobacco (34% vs. 55%), alcohol (23% vs. 41%) or illicit drugs (23% vs. 42%) during pregnancy.

There were no significant differences in the frequencies of stillbirth or other adverse pregnancy outcomes between women who had received monotherapy and those who had received multiple drug treatment. Commonly encountered complications were low birth weight (13-17%), premature delivery (15-16%) and possibly abnormal one-minute Apgar score (11-12%). Among women who had used combined drug therapy, the rates of adverse outcomes for those who had taken protease inhibitors and those who had not were similar, with the exception of the rate of low birth weight, which was higher among users of protease inhibitors (20% vs. 11%). The stillbirth and complication rates of treated and untreated women were also similar; only the rate of premature delivery differed significantly between groups (16% vs. 20%). However, after adjustment for CD4+ cell count and use of tobacco, alcohol and illicit drugs, all rates were similar for those who had received any drug treatment, any combination therapy or no treatment.

Logistic regression analyses that corrected for risk factors such as CD4+ cell count, age, race or ethnicity, and use of tobacco, alcohol or illicit drugs revealed that the risks of premature or very premature delivery and low or very low birth weight for women who had used any combined drug regimen were similar to those for women who had used monotherapy. The risks of premature and very premature delivery that were associated with the use of regimens containing protease inhibitors were similar to those conferred by use of monotherapy or combination therapy without protease inhibitors. Compared with women who had used monotherapy, those who had received combination therapy without protease inhibitors had a lower risk of delivering a low-birth-weight infant (odds ratio, 0.6), whereas women whose regimen had included these drugs had an increased risk of having a very low birth weight infant (2.9). However, these results became nonsignificant after further adjustment for prior premature delivery. Among women who had been given combination therapy, users of protease inhibitors were more likely than nonusers to deliver a baby of low birth weight or very low birth weight (2.3 and 3.2, respectively); the odds of very low birth weight

remained elevated when results were adjusted for prior premature delivery (3.6).

Finally, the investigators compared treated and untreated women and found that those who had used monotherapy or combination therapy with or without protease inhibitors were, in general, as likely as untreated women to have a premature or very premature delivery or a baby of low or very low birth weight. Although users of combination therapy that included protease inhibitors had an elevated likelihood of delivering a baby of very low birth weight (3.2), this result became nonsignificant after adjustment for prior premature delivery. Women whose combination treatment did not include protease inhibitors had a lower likelihood of low birth weight than did untreated women (0.4), even after correction for prior premature delivery (0.5).

According to the authors, the study shows that the risk of adverse birth outcomes associated with administration of antiretroviral combination therapy to manage HIV infection

during pregnancy is no greater than the risks associated with monotherapy or no therapy. Among women who use combination therapy, however, users of protease inhibitors may be at an increased risk of very low birth weight—a finding that the analysts suggest requires confirmation because of its wide confidence interval, the small number of infants involved (a total of 16) and the lack of adjustment for the different study sources. The authors also note that they did not consider other factors such as maternal disease status, HIV viral load, and the precise timing and duration of therapy. They conclude, nevertheless, that “the risks of adverse outcomes of pregnancy that are attributable to antiretroviral therapy are low and are likely to be outweighed by the recognized benefits of such therapy during pregnancy.”—*T. Lane*

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tute, whether they had used a condom with their regular partner, the frequency of condom use with prostitutes and their current partner's number of lifetime partners.

Of the 847 uncircumcised men who had valid results in tests for penile HPV infection, 20% were positive for the virus, whereas only 6% of the 292 circumcised men with valid test results had the infection. The presence of HPV was consistently less prevalent among circumcised men than among uncircumcised men when the two groups were stratified according to the various characteristics. After the analysts made adjustments for potentially confounding factors (including study location), logistic regression analysis showed that the odds of penile HPV infection for circumcised men were about 60% lower than those for uncircumcised men, whether the circumcision status was self-reported or medically confirmed (odds ratio, 0.4 for each). Furthermore, men who had had six or more lifetime partners were more likely than those who had had five or fewer partners to have a diagnosis of penile HPV infection (odds ratio, 2.0).

Analysis of the effect of circumcision status on the prevalence of cervical cancer suggested that circumcision may reduce the likelihood of cervical cancer in the men's current partners (odds ratio, 0.7); however, this result was not statistically significant. Circumcision status did not affect the odds that women had cervical cancer, regardless of women's age, age at first sex, educational level, number of lifetime partners or condom use. When the researchers limited their analysis to the 1,420 monogamous women, they found that the odds of having cervical cancer were reduced by about 60% among women with a partner who reported six or more lifetime sexual partners and had been circumcised (0.4).

The investigators also studied the effect of circumcision on the risk of cervical cancer according to males' level of risky sexual behavior. They classified males who reported six or more lifetime partners and an age at first sex of below 17 as having a high risk, those reporting five or fewer partners and an age at first sex of at least 17 as having a low risk, and the remainder as having an intermediate risk. Circumcision of low-risk men did not reduce women's risk of cervical cancer (odds ratio, 1.6). However, circumcision was linked to reductions in the risk of cervical cancer as the men's sexual behavior got riskier (odds ratios for women whose circumcised partners had intermediate and high risk were 0.5 and 0.2, respectively).

## Male Circumcision Reduces Risk of Both Acquiring And Transmitting Human Papillomavirus Infection

Circumcised men are less likely than uncircumcised men to have penile human papillomavirus (HPV) infection, and female partners of men who engage in risky sexual behavior have a reduced likelihood of having cervical cancer if the man is circumcised. According to a multinational study conducted by the International Agency for Research on Cancer (IARC), the odds that circumcised men had penile HPV infection were about 60% lower than the odds that uncircumcised men had this diagnosis.<sup>1</sup> Among monogamous women who had a partner reporting six or more lifetime sexual partners, the odds of having cervical cancer were reduced by about 60% if the partner had been circumcised.

Recognizing that cervical cancer is the second most common cancer among women worldwide and that nearly all cases may be caused by HPV, the IARC Multicenter Cervical Cancer Study Group sought to investigate how circumcision affects the risks of genital HPV infection in men and cervical cancer in their partners. The researchers conducted a total of seven case-control studies between 1985 and 1993 in Spain, Colombia, Brazil, Thailand and the Philippines. They used a standardized questionnaire to interview women who had newly diagnosed, histologically con-

firmed cervical carcinoma in situ or invasive cervical cancer, as well as age-matched women without these forms of cancer. The investigators also enrolled each partner with whom these women had had regular intercourse for at least six months before the study. These men were administered a similar questionnaire and were tested for penile HPV infection.

The analyses were based on 1,913 male respondents—977 partners of women with cervical cancer and 936 partners of control women. Roughly half of the men were aged 38–56, about one-quarter were 37 or younger and the remainder were 57 or older. The women were distributed about equally among three age-groups—36 or younger, 37–48, and 49 or older. Nineteen percent of the men reported that they were circumcised.

Medical examination of about two-fifths of the men showed that 95% had reported their circumcision status correctly. Circumcised men had a marginally significantly higher educational level than did uncircumcised men; they also were less likely to report genital washing after intercourse but more likely to have good genital hygiene. The two groups of men were no different in the following characteristics: age, age at first sex, number of lifetime partners, whether they had had sex with a prosti-

The authors of an accompanying editorial point out that the strengths of this study are its size, the HPV detection method used (polymerase chain reaction assay) and the generalizability of the findings because of the multiple study locations.<sup>2</sup> They note, however, that some confounding factors are difficult to measure accurately and control for, such as frequency of genital washing and genital hygiene. Furthermore, although the investigators focused on monogamous women, they cannot exclude the possibility that women with cervical cancer had been infected with HPV by an earlier, unreported partner; hence, the association between circumcision and the risk of cervical cancer may have been underestimated.

The researchers suggest that circumcision may reduce the risk of acquiring and transmitting HPV and hence the risk of cervical cancer. They propose that circumcision reduces the vulnerability of the penis to HPV infection: In uncircumcised men, the inner surface of the

foreskin offers a portal of entry for HPV when it is exposed, by way of tiny ulcers and abrasions that occur during intercourse. The authors of the editorial emphasize that circumcision itself does not protect against cervical cancer: The protective effect relates only to a reduction in the likelihood of genital infection with oncogenic HPV in men. Regarding other potential health benefits of circumcision, the investigators recommend that “further study is needed to determine whether routine circumcision can reduce the risks of HIV and HPV infections and other sexually transmitted diseases.”—*T. Lane*

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## Vietnamese Women with Symptoms of Reproductive Tract Infections Often Forgo Care or Treat Themselves

Nearly half of women surveyed in a northern Vietnamese province had had symptoms of reproductive tract infection within the previous six months, but only about two-thirds of these had sought medical care.<sup>1</sup> One-quarter of women with symptoms ignored them, and one in 10 treated themselves. Women who did not perceive their symptoms as signs of illness and women whose symptoms were mild were among those with elevated odds of ignoring their symptoms. Although not all reproductive tract infections are acquired sexually, women who attached stigma to sexually transmitted infections (STIs) also had an increased likelihood of ignoring symptoms.

The survey was conducted in 1998 among a randomly selected sample of women aged 18–49 living in two villages—one urban and one rural—in Hai Phong Province. Virtually all (99%) of the 1,163 participants were married, and about half were using modern contraceptives; the IUD and condoms accounted for the bulk of modern method use (51% and 31%, respectively). Half of the women had had at least one abortion.

Participants reported little in the way of behavior that would increase their risk of STIs. Only 1% said that they had had premarital sex, and 2% reported having had more than one partner. Likewise, 95% said that their husband

had never had another partner, and 4% had ever seen a potential STI symptom in their husband. Most of the women believed that individuals who contract STIs are personally responsible for their infection and that getting an STI would make them feel ashamed.

Forty-four percent of participants reported that within the previous six months, they had had at least one symptom of reproductive tract infection on a list created by the researchers. In this group of women, 78% had had abnormal vaginal discharge, 47% lower abdominal pain, 35% genital itching and 15% pain during intercourse. Smaller proportions (1–4%) reported a variety of other symptoms.

Overall, 64% of women who had had symptoms suggesting the presence of a reproductive tract infection had sought medical care: 25% from a local health station, 16% from a hospital, 15% from a pharmacy and 8% from a private doctor. While 11% had treated themselves, 25% had ignored their symptoms.

Using stepwise logistic regression analysis, the researchers explored the factors that were independently associated with ignoring symptoms of reproductive tract infection. The results showed that women who did not link their symptoms to the possibility of infection were significantly more likely than those who did to neither seek medical care nor treat them-

selves (odds ratio, 3.6); the odds of ignoring symptoms also were elevated among women who had experienced no or mild itching (3.0) and those who had first noticed symptoms within the past week (2.5).

Two social factors also were associated with an increased likelihood of ignoring symptoms: not having sought advice about the symptoms from one's support network (odds ratio, 2.9) and stigmatizing STIs (1.8). Women whose husbands traveled more than eight weeks a year were significantly less likely than those whose husbands spent less time away from home to ignore symptoms (0.3).

Successful management of reproductive tract infections, the researchers comment, “hinges on women's interpretation of and health-seeking behavior for...symptoms.” Thus, the investigators recommend the development of interventions to raise awareness of these infections and their health consequences. They also stress the importance of education focused on reproductive tract infections that are not transmitted sexually, as a means of reducing stigma and thereby encouraging women to seek treatment for symptoms.—*D. Hollander*

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## Treatment of HIV-Positive Pregnant Women Lowers Infection Risk of Infants

When HIV-positive women are treated in late pregnancy and during labor with a short course of zidovudine, their child's likelihood of later becoming infected with HIV is significantly reduced, even when that child has been breastfed.<sup>1</sup> Overall, about two years after being born, children of HIV-infected mothers who had been treated with zidovudine around the time of delivery were about 25% less likely to be HIV-positive than children of women who had received a placebo. The protective effect of zidovudine treatment, however, could be detected only among the children of women who had had higher levels of circulating CD4 cells at study enrollment; the relative reduction in HIV risk among these children was about 60%. In contrast, mother-to-child transmission was unaffected when the mothers had had lower circulating levels of CD4 cells, indicating more advanced immunosuppression.

Postnatal maternal transmission of HIV to a newborn child is a continuing problem in the developing world, particularly in areas such as Africa where breastfeeding is common. Research has shown that maternal use of the drug zidovudine around the time of delivery substantially reduces mother-to-child transmission of HIV when the mother is not breastfeeding her newborn. The long-term benefits of zidovudine treatment are not as clear, however, for breastfed infants.

To assess zidovudine's effectiveness at preventing maternal transmission of HIV in a breastfeeding population, researchers pooled data collected in two studies conducted by France's National AIDS Research Agency (ANRS), the Côte d'Ivoire Ministry of Health and the U.S. Centers for Disease Control and Prevention (CDC). Both were double-blinded, placebo-controlled randomized trials: One, sponsored by the ANRS, was conducted in Abidjan, Côte d'Ivoire, and in Bobo-Dioulasso, Burkina Faso; the other, sponsored by the CDC, took place only in Abidjan.

Pregnant HIV-positive women were recruited to participate in the studies between September 1995 and February 1998. Beginning at 36–38 weeks of gestation, all were instructed to take a tablet (either 250 or 300 mg of zidovudine or a placebo) twice per day until labor began. At this point, the studies diverged slightly: In the ANRS study, women in the treatment group took one dose of 500–600 mg of zidovudine during labor and then took the same amount each day for seven days after delivery; in the CDC study, women in labor were given 300 mg of zidovudine every three hours until they delivered their baby, but received none thereafter. The newborns were not treated in either study.

Researchers performed lymphocyte counts on blood samples taken from the women at enrollment. Blood was taken from the infants one week after delivery, at age four or six weeks, at three months of age and every three months thereafter. Blood samples were tested for the presence of HIV DNA; infants were deemed

HIV-negative if they had no evidence of infection 60 days or more after breastfeeding had ended.

Over the period of the study, the researchers enrolled 701 pregnant HIV-positive women (421 in the ANRS study and 280 in the CDC study). Of these, 678 delivered and 23 were lost to follow-up. When stillbirths and second births among twin deliveries were excluded, there were 662 live-born infants. HIV status could not be determined for 21 of these children. Among the remaining 641 infants, 13 had been bottle-fed from birth or their age at weaning was unknown, leaving 628 breastfed children. Nearly half of the mothers in the study had had CD4 cell counts at enrollment of fewer than 500 per ml, a level indicative of advanced immune system disruption.

By two years after delivery, 68 children born to 319 women who had received zidovudine were HIV-infected, compared with 94 children born to 322 women who had been given a placebo. The cumulative proportions of children who were HIV-infected were 23% in the zidovudine group and 30% in the placebo group. Thus, use of zidovudine appears to have reduced the overall risk of HIV transmission by 26%.

When the researchers examined the results according to the mothers' CD4 counts, however, they found a substantial difference. Among women who had had lower levels of CD4 cells (fewer than 500 per ml) when they entered the study, the 24-month HIV infection levels among their children did not differ by treatment status: 40% in the treatment group and 41% in the placebo group. In contrast, infection rates at 24 months among children whose mothers had had higher CD4 levels (at least 500 per ml) were significantly lower in the treatment group (9%) than in the placebo group (22%). Thus, in this group, the efficacy of zidovudine treatment in reducing the overall risk of mother-to-child HIV transmission appears to have been 59%. There was no difference between the two trials in the impact of treatment.

Overall mortality was substantially lower at 24 months among the children whose mothers had been treated with zidovudine than among those whose mothers had received a placebo. Thirty-nine children in the treatment group had died by 24 months after birth (12%), compared with 68 children in the placebo group (21%).

The researchers observe that the efficacy of zidovudine in preventing HIV-1 infection or death was similar to its efficacy in preventing infection alone. In addition, they point out that the risk of postnatal transmission from untreated mothers with lower prepartum CD4 counts at study enrollment was substantial, while the risk of transmission from untreated mothers with higher CD4 counts was relatively low.

"It is indeed encouraging," the investigators comment, "to confirm a substantial reduction of mother-to-child transmission in breastfeeding women with high CD4 cell counts." They also note, however, that "continued antiretroviral therapy for mothers after giving birth, and perhaps also for their infants, should be considered, especially for mothers with lower CD4 cell counts." They warn that the efficacy of a short-course zidovudine regimen for breastfeeding African women with somewhat advanced immunodeficiency may be limited, and that the overall public health impact of such treatment may depend on the level of immunodeficiency in the population. Nevertheless, while further study of different regimens is necessary, they conclude that "wide-scale implementation of programs to prevent mother-to-child transmission of HIV-1 in Africa should not be delayed, as there are already many obstacles to surmount" if recently promulgated United Nations goals for reduction of mother-to-child transmission are to be achieved.—*M. Klitsch*

#### REFERENCE

I. Leroy V et al., Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa, *AIDS*, 2002, 16(4):631–641.