Brief Report

Prenatal and Postpartum Zidovudine Adherence Among Pregnant Women with HIV

Results of a MEMS Substudy from the Perinatal Guidelines Evaluation Project

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Summary: Adherence to HIV treatment regimens during pregnancy may affect efforts to eliminate vertical transmission and influence the emergence of drug-resistant HIV strains that can affect maternal health and the risk of vertically-transmitted resistant strains. Study objectives were to document patterns of adherence to zidovudine (ZDV) during the perinatal period. Pregnant women with HIV who were seen at public clinics, taking ZDV, and willing to use Medication Event Monitoring Systems (MEMS) caps participated in this adherence substudy. Fifty-three women were included in prenatal analyses; however, 19 women were excluded from postnatal analyses because medical records failed to confirm a postpartum maternal prescription for ZDV. Adherence to ZDV, defined as doses per day taken/prescribed during the last 3 weeks of pregnancy, was extremely low (mean = 50.0%), and declined significantly 3 weeks postpartum (mean = 34.1%) (p = .004). Clinical emphasis must be placed on enhancing adherence during and particularly after pregnancy when ZDV is continued for a mother's own care. Key Words: HIV/AIDS—Adherence—Women—Pregnancy—Medication Events Monitoring System (MEMS).

Among women, HIV infection is often diagnosed and treatment is instituted during pregnancy (1). Adherence to treatment regimens during pregnancy may affect ef-

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The Perinatal Guidelines Evaluation Project was funded by the Centers for Diseases Control and Prevention through Cooperative Agreements to the following universities: Yale University (U64/CCU 12274), State University of New York, Health Science Center at Brooklyn (U64/CCU 21267), Duke University (U64/CCU 412273) and the University of Miami (U64/CCU 412294).

Manuscript received November 26, 2001; accepted March 25, 2002.
records the precise date and time that a pill vial is opened and, presumably, when the drug is taken. MEMS caps may provide one of the most accurate measures of adherence, because they do not rely on self-report, which may be compromised by poor memory and desire to please investigators, pill counts that can be manipulated, or serum levels that reflect only recent adherence (2). Results of this study may provide important information for the development of clinical interventions to improve adherence, thus protecting women from the development of medication resistance and reducing rates of HIV transmission from mother to child.

METHODS

Study Participants

Pregnant women receiving prenatal care at publicly funded health clinics were enrolled in the Perinatal Guidelines Evaluation Project (3), a CDC-funded study designed to examine biomedical and psychosocial factors unique to HIV and pregnancy. Women eligible for this adherence substudy were prescribed zidovudine (ZDV) or Combivir (combined dose of ZDV/3TC) (GlaxoSmithKline, Research Triangle Park, NC, U.S.A.), agreed to use the MEMS cap, and enrolled in the study between July 1997 and September 1998. Sixty-five women met these entry criteria; of these, 57 women returned the MEMS caps. (There were 264 women from the primary study who participated in a follow-up interview at approximately 32 weeks gestational age; distribution of MEMS caps was conducted at this interview. The small subset of patients enrolled in this MEMS substudy reflects the fact that this substudy was initiated 1 year after the interviews commenced.) Participants came from four geographic locations: Brooklyn, New York (n = 22), Miami, Florida (n = 17), Connecticut (n = 12), and North Carolina (n = 6). Fifty-three (81.5%) women were included in prenatal analyses because medical record review confirmed a prescription to ZDV/Combivir and participants opened their MEMS caps at least one time, indicating that they used the device. Nineteen women were excluded from postnatal analyses because their medical record review failed to confirm a postpartum maternal prescription for ZDV/Combivir.

Data Collection and Study Instruments

Procedures, including informed consent, were approved by Institutional Review Boards at each site and at the Centers for Disease Control and Prevention. Participation was voluntary and did not influence healthcare delivery.

Medication Event Monitoring System

MEMS caps were distributed at study entry during the third trimester of pregnancy and retrieved 6 weeks postpartum. Results presented rely on data from 3 weeks prenatal through 3 weeks postpartum. The primary measure of adherence was based on doses per day, and was calculated using the ratio of doses taken to doses prescribed. Therapeutic coverage was used as a supplementary measure to reflect the percent of time per 24-hour day that an individual maintained active medication coverage based on the precise time the medication cap was opened. For example, if an individual was prescribed dosing 2 times per day, it was assumed that the MEMS cap should be opened at 12-hour intervals; if the bottle was opened at 7:00 AM and then not again until 11:00 PM, therapeutic coverage would be 83%, reflecting coverage for 20 out of 24 hours of that particular day.

Medical Record Review

Centrally trained staff reviewed medical records to obtain prenatal and postnatal medication regimens. All participants except 2 were administered oral/intravenous ZDV during labor and delivery.

Structured Interviews

Structured interviews were conducted by centrally trained study interviewers during the third trimester of pregnancy at prenatal sites. Background information included sociodemographics, pregnancy/family history, and a brief medical history.

Data Analyses

Patient characteristics, patterns of prescribing medication, and adherence were described for the study sample. Comparisons between those who were included in postnatal analyses were compared with those excluded using t tests and likelihood ratio X2 statistics. Mean (SD) and median (25th, 75th percentiles) values of adherence and therapeutic coverage were described for the 6-week period of the study (i.e., 3 weeks prenatally and 3 weeks postnatally). A Wilcoxon signed rank test was conducted to determine whether there was a statistically significant decline in adherence from the prenatal to postpartum periods. In addition, a paired samples t test was also conducted to look at differences at the individual level. Statistical analyses were conducted using SPSS for Windows 10.0 (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Description of Study Sample

Study participants ranged in age from 16 to 42 years (mean = 27.7, SD ± 6.2); 68% were African American, and 22% were Latina. One half had not completed high school; 74% were not employed; and 59% reported a monthly household income of US$1000 or less. Most (82%) received Medicaid coverage for prenatal care. Eighty-six percent had one or more prior pregnancies. Thirty-seven percent of women learned of their HIV infection during the index pregnancy, and 39% reported a history of ZDV prior to the index pregnancy. Nineteen women were excluded from postnatal analyses because the medical record review failed to confirm a postpartum maternal prescription for ZDV or Combivir. There were no significant differences in prenatal adherence or baseline sociodemographic characteristics (e.g., age,
race/ethnicity, employment, HIV diagnosis before vs. during pregnancy) between those who remained in the study for postpartum analyses and those who were excluded (all \( p > .05 \)).

**Patterns of Prescribing Medications and Adherence to ZDV**

All women were prescribed ZDV or Combivir—the treatment recommended to prevent perinatal transmission by established clinical guidelines at that time—to be eligible for the substudy. Fifty-six percent of women were prescribed this medication 1–2 times per day, and the remainder were prescribed ZDV 3–5 times per day. Medical records data also indicate that 70% of women were taking at least one other antiretroviral or prophylactic medication at their last prenatal care visit (e.g., didanosine, lamivudine, stavudine). Note that nevirapine was not routinely prescribed for pregnant women during the time period of this study; only 2 women were prescribed nevirapine prenatally and 5 women were prescribed nevirapine postpartum.

Figure 1 illustrates the distribution of patients by mean dose adherence categories for the 6-week study period. Adherence ranged from 0%–100% across patients in both the prenatal and postpartum periods. Only a small proportion of patients took 76%–100% of doses each week of the study period, ranging from 21%–41% during each of the three prenatal weeks to only 14%–23% during each of the three postpartum weeks. The proportion of patients with "0% adherence" (i.e., took no ZDV) increased steadily from 3 weeks prenatal to 3 weeks postpartum. Eighteen percent of patients took no ZDV 3 weeks prenatal, with an increase to 41% of patients who took no ZDV 3 weeks postpartum. There was a statistically significant decline in adherence from the prenatal to postpartum period (Wilcoxon signed rank test \( z = -2.87, p = .004 \); and for patients with both pre- and postnatal adherence scores \( n = 31 \), paired sample \( t = 3.31, p = .002 \)).

![Graph showing adherence over weeks](image)

**FIG. 1**. Zidovudine (ZDV) adherence in the perinatal period. Proportion of women at five levels of weekly individual mean ZDV dose adherence (0%, 1%–25%, 25%–50%, 51%–75%, 76%–100%) during the perinatal period, and the mean (± SD) and median (25th, 75th percentile) for adherence by dose and therapeutic coverage.
Mean prenatal adherence was 50.0% (SD = 32.6). The week before delivery had the lowest mean adherence of the three (40.5%). Mean postpartum adherence was 34.1% (SD = 31.0), with the week after birth having the lowest average adherence rate (29.3%). Median adherence 2–3 weeks prenatally was > 60% (i.e., 66.7% 3 weeks prenatal and 62.2% 2 weeks prenatal) and dropped to 35.7% in the week immediately prior to the birth. Excluding patients with no confirmed medical record of a ZDV prescription postpartum (n = 19), median postpartum adherence was 29.5%, with a 25th percentile of 0% throughout the 3 weeks postpartum, indicating that at least one quarter of patients took no ZDV/Combivir.

Patterns for therapeutic coverage were similar to those seen for percentage of doses taken, though mean values were lower than dose adherence. Therapeutic coverage values indicated that women received adequate dosing of ZDV for an average of 10.1 hours per day prenatally and 6.5 hours per day postpartum.

The study sample was too small to conduct a thorough investigation of predictors of adherence. However, post hoc analyses revealed that in the prenatal period, those who were prescribed ZDV only 1–2 times per day had significantly higher adherence than those prescribed ZDV 3–5 times per day (58.1% vs. 40.3%, respectively, p = .05). There was no difference in postpartum adherence based on regimen dosing (1–2 times per day vs. 3–5 times per day). There were no differences in adherence based on study site.

**DISCUSSION**

Adherence to ZDV or Combivir (ZDV/3TC) during late pregnancy was extremely low and declined significantly postpartum for women seen for care at public clinics. Most women in this study were prescribed ZDV for the first time during this index pregnancy. When combined with other medications, ZDV provides an important first line of defense against HIV disease progression that should not be compromised by nonadherence. However, for women in the immediate prenatal and postpartum periods, adherence to complex treatment regimens may be more difficult as a result of the physical and emotional demands of pregnancy and the responsibilities of infant care. It is notable that 18% of women took no ZDV in the week immediately before delivery, given evidence that abbreviated treatment close in time to delivery may be most critical to prevent perinatal transmission of HIV (4.5), These data build on a review of pharmacy claims among pregnant women who were enrolled in New York State Medicaid and who were prescribed ZDV: on the basis of pharmacy measures, only 34% of women refilled enough ZDV prescriptions to cover at least 80% of their doses prenatally (6), and this declined to 28% in the postnatal period (7).

Current treatment guidelines recommend that pregnancy is not a reason to defer standard therapy (5,8). If a patient is unable to adhere to her treatment regimen, clinicians must consider additional efforts to enhance adherence during the perinatal period. This is critical to maximally suppress viral load at delivery and reduce the emergence of resistance. Maintaining adherence postpartum is also important, because many women experience a gap between obstetrical care and medical care in the immediate postpartum period.

This is one of the first studies to examine adherence among pregnant women with HIV. MEMS caps provide an advantage because they record the precise date and time that a pill vial was opened. However, it is assumed that one dose is taken with each bottle opening, and this may under- or overestimate actual dose taken (2). At least 2 clinical studies have documented barriers to the use of MEMS, such as pill decanting (removing >1 dose at a time), which can result in underestimates of adherence (9,10). We took a conservative approach by excluding patients from analyses if a woman never used the MEMS cap in a given week (i.e., rather than give her a score of “0% adherence”). Patients were also excluded if medical records could not confirm a postpartum ZDV prescription. On the other hand, it is possible that some women had discontinued therapy as per physician recommendation but were included in analyses. Moreover, lower levels of adherence 1 week before and 1 week after birth may be a function of other factors, such as time spent in the hospital, where medications would be administered by medical personnel (i.e., and therefore not recorded using the MEMS cap devices). Finally, this study was limited by its small sample size and the reduction in sample size for the postpartum analyses; therefore, we were unable to investigate predictors of adherence. Results must be replicated with women in other clinical settings to ensure generalizability.

Patient adherence is a critical component of successful HIV treatment and prophylaxis. Although combination antiretroviral therapy is effective in slowing disease progression, the long-term benefit of these therapies can only be sustained if resistant HIV strains do not emerge. Future research must identify risk factors associated with non-adherence among pregnant and postpartum women with HIV; in turn, intervention programs to promote adherence must be evaluated in controlled clinical studies. Strategies to increase medication adherence in this population could include education regarding the importance of adherence for the prevention of HIV transmission.
reminder systems (e.g., beepers, pill boxes), regimen 
simplification if possible, and monitoring of adherence 
and barriers to adherence to tailor solutions for indi-
vidual patients (3). Medication adherence is complex; 
therefore, comprehensive and individualized interven-
tions appear to be required to enhance pill-taking behav-
ior (11). However, the feasibility of implementing these 
complex interventions in non-research settings where re-
sources are limited has yet to be determined. Results of 
such research and clinical intervention will contribute to 
efforts to prevent HIV viral breakthrough and vertical 
transmission, enhancing the health of both women and 
their children.

Acknowledgments: Investigators of the Perinatal Guide-
lines Evaluation Project include the authors plus addi-
tional investigators from Yale University (Kathleen Ethier), State Uni-
versity of New York, Health Science Center at Brooklyn (Jack 
Dehovitz), University of Miami School of Medicine (Mary Jo 
O’Sullivan), Duke University (Emmanuel Walter), and the 
Centers for Disease Control and Prevention (Daphne Cobb, 
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Daniel Whittaker).

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