Antimicrobial Agents and Chemotherapy

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Antiretroviral Concentrations in Breast-Feeding Infants of Mothers Receiving Highly Active Antiretroviral Therapy

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Drugs administrated to nursing mothers during the first 6 months after delivery. There are limited data describing the concentrations of zidovudine, lamivudine, and nevirapine in nursing infants as a result of transfer via breast milk. The Kisumu Breastfeeding Study is a phase IIb open-label trial of prenatal, intrapartum, and postpartum maternal treatment with zidovudine, lamivudine, and nevirapine from 34 weeks of gestation to 6 months postpartum. In a pharmacokinetic substudy, maternal plasma, breast milk, and infant dried blood spots were collected for drug assay on the day of delivery and at 2, 6, 14, and 24 weeks after delivery. Sixty-seven mother-infant pairs were enrolled. The median concentrations in breast milk of zidovudine, lamivudine, and nevirapine during the study period were 14 ng/ml, 1,214 ng/ml, and 4,546 ng/ml, respectively. Zidovudine was not detectable in any infant plasma samples obtained after the day of delivery, while the median concentrations in infant plasma samples from postpartum weeks 2, 6, and 14 were 67 ng/ml, 32 ng/ml, and 24 ng/ml for lamivudine and 987 ng/ml, 1,032 ng/ml, and 734 ng/ml for nevirapine, respectively. Therefore, lamivudine and nevirapine, but not zidovudine, are transferred to infants via breast milk in biologically significant concentrations. The extent and effect of infant drug exposure via breast milk must be well understood in order to evaluate the benefits and risks of maternal antiretroviral use during lactation.

The administration of antiretroviral agents during pregnancy and around delivery has been shown to be effective in reducing mother-to-child transmission of human immunodeficiency virus (HIV) (6). However, transmission of HIV from mother to child after birth via breast milk remains a major problem in areas of the world where formula feeding is not safe, affordable, or practical (5, 23). The extension of maternal highly active antiretroviral therapy (HAART) through the period of breast feeding has been proposed as one strategy to reduce breast milk HIV transmission by reducing plasma and breast milk HIV concentrations and/or by providing prophylaxis to the infant through ingestion of antiretrovirals present in breast milk (33). Previous human studies have shown that antiretrovirals administered to nursing mothers are present in their breast milk, but the extent of antiretroviral transfer from mother to infant via breast milk and the resulting infant antiretroviral drug exposure have not been well delineated (4, 7, 19, 21, 26, 27). The aim of this study was to describe antiretroviral concentrations in maternal plasma, breast milk, and infant dried blood spots during the administration of combination antiretroviral therapy to nursing mothers during the first 6 months after delivery. (This study was presented in part at the 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, CA, 27 February 2007.)

MATERIALS AND METHODS

The Kisumu Breastfeeding Study is a phase IIb open-label clinical trial in Kisumu, Kenya, sponsored by the Centers for Disease Control and Prevention (CDC), the Kenya Medical Research Institute (KEMRI), and the Kenya Ministry of Health (31). Pregnant HIV-infected women enrolled in the trial received HAART with lamivudine and zidovudine plus either nevirapine or nelfinavir for prevention of mother-to-child HIV transmission starting at 34 to 36 weeks of gestation, continuing through labor and delivery, and for 6 months postpartum. This analysis presents data on women who received nevirapine-based HAART, consisting of lamivudine and zidovudine administered as a fixed-dose combination (Combivir) in 1 tablet twice a day and nevirapine (Viramune) at 200 mg once daily for 14 days, followed by 200 mg twice a day. Infants received single doses of 2 mg/kg of body weight of nevirapine within 72 h of birth. Mothers were instructed to exclusively breast feed their infants and then to start weaning at 5½ months postpartum. Maternal plasma, breast milk, and infant dried blood spots were collected from a nonrandom subset of sequentially enrolled subjects participating in a breast milk substudy. Informed consent for participation in the main study and for participation in the substudy was obtained from all study mothers. The protocol was approved by the CDC, KEMRI, Boston University Medical Center, and University of California at San Diego human study committees.

Maternal plasma and breast milk samples and infant dried blood spots were collected within 24 h of delivery and at four postpartum study visits (2, 6, 14, and 24 weeks after delivery). Dried blood spot samples were collected based on procedures described by Mei et al. (15) All infant single nevirapine doses were administered after the day-of-delivery sample had been collected. All study nevirapine was dispensed in pill bottles with Medication Event Monitoring System caps (Aardex, Ltd., Union City, CA), which were used to determine the dosing times for the last three maternal antiretroviral doses prior to sampling; timing was confirmed by pharmacy staff for both nevirapine and zidovudine/lamivudine through interview of the women. The three most-recent infant feed-
The dried blood spot concentrations for each antiretroviral at each study visit are presented numerically in Table 1 and graphically in Fig. 1. Maternal plasma and breast milk antiretroviral concentrations were measured at each study visit and are presented in Table 1. The median birth weight of the study infants was 3,000 g (range, 2,200 to 4,000 g). The median maternal age was 24.5 years (range, 18.1 to 37.0 years), and the median maternal weight was 57.5 kg (range, 44.3 to 73.1 kg). There were 28 female infants and 39 male infants. The median infant birth weight was 3,000 g (range, 2,200 to 4,000 g).

The dried blood spot concentrations for each antiretroviral at each study visit are presented numerically in Table 1 and graphically in Fig. 1. Maternal plasma and breast milk concentrations were measured at each study visit and are presented numerically in Table 1 and graphically in Fig. 2 and 3. Zidovudine concentrations were assayed in non-randomly selected groups of 82 infant dried blood spots, 45

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**TABLE 1. Zidovudine, lamivudine, and nevirapine concentrations and IQRs in dried blood spots from infants in the Kisumu Breastfeeding Study, Kenya, 2004 to 2007**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Delivery</th>
<th>Median concn (ng/ml) (IQR)</th>
<th>no. of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Wk 2</td>
<td>24* (16–40)</td>
<td>24*† (15–29)</td>
</tr>
<tr>
<td></td>
<td>Wk 6</td>
<td>20* (15–29)</td>
<td>20*† (15–29)</td>
</tr>
<tr>
<td></td>
<td>Wk 14</td>
<td>303* (150–444)</td>
<td>303*† (150–444)</td>
</tr>
<tr>
<td></td>
<td>Wk 24</td>
<td>987* (790–1,017)</td>
<td>987*† (790–1,017)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Wk 2</td>
<td>22* (16–40)</td>
<td>22*† (15–29)</td>
</tr>
<tr>
<td></td>
<td>Wk 6</td>
<td>17 ng/ml</td>
<td>17 ng/ml</td>
</tr>
<tr>
<td></td>
<td>Wk 14</td>
<td>43 ng/ml</td>
<td>43 ng/ml</td>
</tr>
<tr>
<td></td>
<td>Wk 24</td>
<td>34 ng/ml</td>
<td>34 ng/ml</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Wk 2</td>
<td>19* (15–29)</td>
<td>19*† (15–29)</td>
</tr>
<tr>
<td></td>
<td>Wk 6</td>
<td>43 ng/ml</td>
<td>43 ng/ml</td>
</tr>
<tr>
<td></td>
<td>Wk 14</td>
<td>50 ng/ml</td>
<td>50 ng/ml</td>
</tr>
<tr>
<td></td>
<td>Wk 24</td>
<td>40 ng/ml</td>
<td>40 ng/ml</td>
</tr>
</tbody>
</table>

* For comparative purposes, the IC50 for wild-type HIV-1, subtype B, for lamivudine is 0.6 to 21 ng/ml and for nevirapine is ~17 ng/ml. +, P < 0.05 compared to results for delivery sample; †, P < 0.05 compared to results for 24-week sample.
maternal plasma samples, and 35 breast milk samples. Sixteen dried blood spots obtained on the day of delivery were assayed, and eight had quantifiable amounts of zidovudine, with a median zidovudine concentration of 24 ng/ml (IQR, below quantifiable limit [BQL] to 76 ng/ml). The zidovudine concentrations in the remaining 66 infant dried blood spots, collected at the 2-, 6-, 14-, and 24-week time points were all below the assay limit of detection. Due to the preponderance of dried blood spot samples with zidovudine concentrations below the assay limit of quantification, no further specimens were assayed for zidovudine.

Lamivudine and nevirapine assay data for an individual visit were included in the final data set if the samples from all three matrices (maternal plasma, breast milk, and infant dried blood spots) were adequate for assay and if the maternal nevirapine and lamivudine concentrations were detectable, indicating that the mother had been adherent with the antiretroviral regimen. A total of 153 visits from 58 (of 67 enrolled) mother-infant pairs met these criteria. The median infant dried blood spot lamivudine concentration was higher on the day of delivery (67 ng/ml) than at week 2 (32 ng/ml), week 6 (24 ng/ml), week 14 (20 ng/ml), or week 24 (BQL). The median infant dried blood spot nevirapine concentration was higher on the day of delivery (2,963 ng/ml) than at week 2 (987 ng/ml), week 6 (1,032 ng/ml), week 14 (734 ng/ml), or week 24 (303 ng/ml).
There were no differences across study visits for median maternal plasma or breast milk concentrations of any of the antiretrovirals. The median maternal plasma zidovudine concentration across all study visits was 23 ng/ml (IQR, 12 to 59 ng/ml). The median breast milk zidovudine concentration was 9 ng/ml (IQR, BQL to 26 ng/ml), and the median ratio of the breast milk-to-maternal plasma zidovudine concentrations was 0.44 (IQR, 0.23 to 0.65). The median estimated infant daily dose of zidovudine (based on an estimated daily breast milk intake of 150 ml/kg/day) was 1.35 g/kg.

The median maternal plasma lamivudine concentration was 508 ng/ml (IQR, 290 to 800 ng/ml). The median breast milk lamivudine concentration was 1,214 ng/ml (IQR, 862 to 1,651), and the median ratio of the breast milk-to-maternal plasma lamivudine concentrations was 2.56 (IQR, 1.79 to 3.89). Over the course of the dosing interval, the rate of decline of the lamivudine concentration in breast milk was slower than in maternal plasma, resulting in an increasing lamivudine breast milk-to-plasma ratio (Fig. 2 and 3). Assuming a daily breast milk intake of 150 ml/kg/day, the median estimated infant daily dose of lamivudine was 182 g/kg.

The median maternal plasma nevirapine concentration was 6,087 ng/ml (IQR, 4,895 to 7,518 ng/ml). The median breast milk nevirapine concentration was 4,546 ng/ml (IQR, 3,480 to 5,715 ng/ml), and the median ratio of the breast milk-to-maternal plasma nevirapine concentrations was 0.75 (IQR, 0.64 to 0.89). Assuming a daily breast milk intake of 150 ml/kg/day, the median estimated infant daily dose of nevirapine was 682 g/kg. The distribution of the number of days required to receive a cumulative 2-mg/kg dose of nevirapine, the infant prophylactic dose administered as part of the single-dose nevirapine regimen, is presented in Fig. 4 (9). The observed infant nevirapine concentrations are plotted against those predicted using our estimates of daily infant nevirapine doses and our previous infant pharmacokinetic model in Fig. 5 (17).

**DISCUSSION**

Our data confirm that the antiretroviral drugs zidovudine, lamivudine, and nevirapine administered to pregnant and nursing women can be measured in the infants’ plasma shortly after birth and in breast milk expressed while nursing. Once the immediate newborn period has passed, lamivudine and nevirapine remain present in biologically significant concentrations in the infants’ plasma, while zidovudine is not detected above the lower limit of quantitation of the assay used. Three previous studies have described concentrations of zidovudine, lamivudine, and nevirapine associated with the administration of HAART to breast-feeding mothers (5, 8, 27). Only one of these studies measured infant antiretroviral concentrations, and in that study, infant treatment with prophylactic daily zidovudine dosing prevented an evaluation of zidovudine exposure due to breast milk alone (27). The data reported here are the first from a cohort of women receiving nevirapine-based HAART and their infants studied on the day of delivery, as well as at several subsequent times over the first 6 months of nursing.

Our data demonstrate that the magnitude of infant drug concentrations from exposure to maternally administered drug differs for each individual antiretroviral agent studied, as well as with the time postpartum. For all antiretrovirals, infant

**TABLE 2.** Zidovudine, lamivudine, and nevirapine concentrations in maternal plasma and breast milk and breast milk-to-plasma ratios in the Kisumu Breastfeeding Study, Kenya, 2004 to 2007

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median concn (ng/ml) (IQR) [no. of samples] in:</th>
<th>Breast milk/plasma ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal plasma</td>
<td>Breast milk</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>23 (12–59) [45]</td>
<td>9 (BQL-26) [35]</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>508 (290–800) [153]</td>
<td>1,214 (862–1,651) [153]</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>6,087 (4,895–7,518) [153]</td>
<td>4,546 (3,480–5,715) [153]</td>
</tr>
</tbody>
</table>

FIG. 4. Proportion of breast-feeding infants receiving a cumulative breast milk nevirapine dose of 2 mg/kg plotted against number of days of breast feeding (estimated from day-of-delivery breast milk nevirapine concentrations), Kisumu Breastfeeding Study, Kenya, 2004 to 2007.

FIG. 5. Observed and model-predicted infant dried blood spot (DBS) nevirapine (NVP) concentrations (conc) at weeks 2, 6, and 14 postpartum, Kisumu Breastfeeding Study, Kenya, 2004 to 2007.
concentrations were highest on the day of delivery compared to the other postnatal sampling times, consistent with transplacental passage of the antiretrovirals from mother to fetus prior to delivery. The infant concentrations of zidovudine, lamivudine, and nevirapine at delivery observed in this study are consistent in magnitude with those seen in other studies reporting infant antiretroviral concentrations at delivery following chronic maternal dosing during pregnancy and labor (18, 19, 24). In our current study, infant lamivudine and nevirapine concentrations declined over the study period despite constant breast milk concentrations, consistent with previously observed developmental increases in nevirapine and lamivudine clearances over the first 6 months of life (17, 32). The decreased drug concentrations at the 24-week visit may have been affected by the initiation of weaning prior to the collection date, though we do not have precise information on when weaning began for each woman.

The infant drug concentrations at the week 2 through week 14 postnatal visits reflect drug exposure from breast feeding during adherent maternal HAART administration and exclusive breast feeding. At these times, maternal plasma zidovudine concentrations were low, reflecting the very short (~1 h) half-life of zidovudine in adults and the resulting rapid clearance of an administered dose from plasma during a dosing interval. The median breast milk-to-plasma ratio for zidovudine was around 50%. While the standard daily zidovudine infant dose used for prevention of mother-to-child transmission in the first 4 to 6 weeks of life is 8 mg/kg (or 8,000 μg/kg), we estimated a median daily infant zidovudine dose from breast milk of 1.35 μg/kg, more than 1,000 times lower than the standard prophylactic dose (3). Given this extremely small breast milk dose, it is not surprising that zidovudine was not detectable in any of the infant samples obtained after the day of delivery. A limitation of our study is that very few of our samples were obtained within the first 2 h after maternal dosing, when maternal plasma and breast milk zidovudine concentrations are highest. We also did not assay for intracellular concentrations of phosphorylated zidovudine in the infants due to the large amount of blood required for this assay. The active form of zidovudine is its intracellular triphosphorylated metabolite, which has a longer half-life than unmetabolized plasma zidovudine. It is possible that some zidovudine may reach the infant from breast milk, entering and persisting inside the cells while plasma concentrations quickly fall below the limit of quantitation of our assay, especially if nursing takes place soon after maternal dosing.

The lamivudine plasma concentrations in the mothers were consistently higher than those of zidovudine, which is consistent with the longer plasma half-life of 5 to 7 h for lamivudine. The lamivudine concentrations in breast milk were generally greater than those in plasma, which is consistent with previous findings (8, 27). Lamivudine concentrations in breast milk declined more slowly than in plasma, leading to a gradual increase in the lamivudine milk-to-plasma ratio as the dosing interval progressed. The change in the lamivudine milk-to-plasma ratio over the course of the dosing interval demonstrates why breast milk and maternal plasma drug concentration data must be analyzed taking into account the time since maternal dosing (34). The estimated infant median daily dose of lamivudine from breast milk was 182 μg/kg, which is approximately 2% of the recommended daily treatment dose of lamivudine of 8 mg/kg divided into two doses in children over 3 months of age. Exposure to this amount of lamivudine via breast milk, as measured from weeks 2 to 24, resulted in a median infant lamivudine concentration of 23 ng/ml, which is just above the upper limit of the range of the lamivudine 50% inhibitory concentration (IC50) for wild-type HIV (0.6 to 21 ng/ml) (4).

Nevirapine has a long half-life (20 to 30 h) with chronic dosing in adults. Maternal nevirapine concentrations were in the range typically seen with chronic nevirapine therapy in adults (10). The median nevirapine breast milk-to-plasma ratio was just over 70% and remained constant over the maternal dosing interval. The median estimated daily dose of nevirapine administered to the infants from breast milk was just over 600 μg/kg/day. Studies investigating the efficacy of direct administration of nevirapine to breast-feeding infants to prevent breast milk HIV transmission are ongoing (13, 20). The dose used in these studies is 4 mg/kg (or 4,000 μg/kg) once a day, and our estimated breast milk dose is about 15% of this dose (29). Using a previously developed model of nevirapine pharmacokinetics in infants, the predicted nevirapine concentrations were somewhat lower than those observed in the current study. This analysis suggests that our estimated dose of presumed daily breast milk intake derived from U.S. data may be conservative, underestimating the actual daily nevirapine dose from breast milk in these Kenyan infants. During weeks 2, 6, and 14, the median infant nevirapine concentration was 896.9 ng/ml, well above the median HIV IC50 of 17 ng/ml for nevirapine but below the suggested target trough nevirapine concentration of 3,000 ng/ml (1; Nevirapine package insert, revised April 2007 [Boehringer Ingelheim]). The maternal plasma, breast milk, and infant concentrations and the breast milk/plasma ratio observed for nevirapine in this study are very similar to those recently reported in a study of efavirenz transfer from breast milk. In that study, the median maternal plasma efavirenz concentration was 6,030 ng/ml, the median breast milk efavirenz concentration was 3,450 ng/ml, the mean efavirenz breast milk/plasma ratio was 0.54, and the median infant efavirenz concentration was 870 ng/ml, just below the suggested target trough efavirenz concentration of 1,000 ng/ml (1, 26). These data suggest that the transfer of either non-nucleoside reverse transcriptase inhibitor from maternal breast milk to infants would have similar potential for beneficial or adverse effects.

The infant nevirapine concentrations we observed in the day-of-delivery samples reflect transplacental passage of nevirapine and were roughly equivalent to those in maternal plasma at the time of delivery. Based on the range of breast milk nevirapine concentrations observed in this study, we estimate that by day 3 of life, 50% of infants ingested from breast milk a total nevirapine dose exceeding the 2-mg/kg infant postnatal prophylactic dose and by day 4 of life, the breast milk nevirapine dose exceeded 2 mg/kg in over 70% of infants. As a result of this combined transplacental and breast milk nevirapine exposure over the course of the first week of life, nursing infants whose mothers received a chronic prenatal and postnatal nevirapine HAART regimen will have nevirapine concentrations that exceed those seen in infants exposed to the mother-infant single-dose prophylactic perinatal regimen. Ad-
administration of the single-dose postnatal infant prophylactic nevirapine may be unnecessary in these infants if the mother is adherent to combination therapy before and after delivery. However, there was no evidence that the nevirapine dose given to the infants in this study was harmful, and programatically it may be difficult to determine which mothers are adherent to ART.

In countries with high per capita incomes where triple-combination antiretroviral regimens, elective cesarean section, and safe formula feeding are readily available and acceptable to pregnant women, rates of mother-to-child transmission as low as 0.6% have been reported (22). In resource-limited settings where some or all of these interventions are not available, the use of shorter, less-intensive antiretroviral regimens has been shown to result in smaller but still very significant reductions in antenatal and intrapartum mother-to-child HIV transmission (7). In resource-limited settings where formula feeding is not safe or practical and breast feeding substantially improves infant survival, prevention of postnatal HIV transmission via breast milk remains a major challenge (33). Although exclusive breast feeding has been shown to be associated with lower rates of HIV transmission than mixed feeding, the risk of transmission is not eliminated. Recent studies of the strategy of exclusive breast feeding for 4 to 6 months followed by early cessation of breast feeding and the use of replacement feeding and complementary foods have been associated with increased risks after weaning of morbidity and mortality from infectious diseases and malnutrition (30). The development of practical and effective strategies to allow continued breast feeding while minimizing the risk of mother-to-child HIV transmission is urgently needed.

One proposed strategy for the prevention of breast milk HIV transmission is the administration of HAART to nursing mothers. Treatment of nursing mothers with zidovudine, lamivudine, and nevirapine from 28 weeks of gestation through 1 month postpartum has been shown to reduce breast milk HIV viral RNA loads at delivery and at the end of the first postpartum week compared to the levels in untreated women, although breast milk HIV DNA may be not be suppressed (8, 28). Several studies of the efficacy of maternal HAART in preventing breast milk HIV transmission are under way. However, animal and human studies have demonstrated that antiretroviral agents are transferred into breast milk (5, 19, 21, 25). Because of the frequency of feeding and the reduced clearance of antiretrovirals in infants, even low concentrations of antiretrovirals in breast milk may result in biologically significant antiretroviral concentrations in the nursing infant (14). An understanding of infant drug exposure resulting from antiretrovirals received via breast milk is necessary before the use of antiretrovirals in nursing women becomes widespread.

Our data clearly show that lamivudine and nevirapine, but not zidovudine, are transmitted in biologically significant concentrations via breast milk to nursing infants when their mothers receive these drugs. The resulting infant antiretroviral drug exposure may have benefits, such as prevention of HIV infection or partial suppression of HIV replication in infants who become HIV infected. Alternatively, this drug exposure could result in potential drug side effects or, in infants who become HIV infected, the emergence of HIV drug resistance. Recent data from the parent Kisumu Breastfeeding Study demonstrate the emergence of HIV type 1 genotypic resistance mutations to nucleoside reverse transcriptase inhibitors (primarily to lamivudine but, to a lesser degree, to zidovudine as well) and nonnucleoside reverse transcriptase inhibitors among children who are HIV infected at birth or during the first 6 months while breast feeding and whose mothers received treatment with zidovudine, lamivudine, and nevirapine during pregnancy and while nursing (35). While enhanced prophylactic strategies such as this are likely to reduce perinatal and postpartum HIV infections among infants, the extent of infant drug exposure via breast milk and the effects on infants of this exposure, especially the emergence of resistance mutations in those infants who become HIV infected despite maternal treatment, are important considerations for HIV treatment programs providing maternal HAART during breast feeding for prevention of mother-to-child transmission and for pediatric treatment programs that treat HIV-infected infants who have been exposed to these drugs via breast feeding.

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M.M., T.T., E.C., P.J.W., and M.C.T. participated in the conception, design, conduct, and data analysis of the project and the writing of the manuscript; C.Z., R.M., and P.O. participated in the design and conduct of the project and the writing of the manuscript; D.H. participated in the conduct and data analysis of the project and the writing of the manuscript, and M.G.F. participated in the conception and design of the project and the writing of the manuscript. The authors declare no conflicts of interest.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention. Use of trade names is for identification purposes only and does not constitute endorsement by the U.S. Centers for Disease Control and Prevention or the Department of Health and Human Services.

The protocol for use of human subjects was approved by the Institutional Review Boards of the Kenya Medical Research Institute, U.S. Centers for Disease Control and Prevention, Boston University Medical Center, and University of California at San Diego.

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