# After AIDS Clinical Trial 076: The Changing Pattern of Zidovudine Use during Pregnancy, and the Subsequent Reduction in the Vertical Transmission of Human Immunodeficiency Virus in a Cohort of Infected Women and Their Infants

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**To determine the impact of the AIDS Clinical Trials Group (ACTG) Protocol 076 results on the subsequent use of zidovudine during pregnancy and the transmission rate of human immunodeficiency virus (HIV) in a cohort of mother-infant pairs (Women and Infants Transmission Study), a retrospective analysis was done. Transmission rates were calculated by simple proportion for infants with at least 6 months of follow-up, stratified by date of birth ($n$ = 453 born on or before 1 March 1994; $n$ = 103 born after 1 March 1994). Transmission rates decreased from 19% to 8% ($P$ = .005, Fisher's exact test). Zidovudine use increased during pregnancy (22% vs. 89%) and in newborns (1% vs. 79%). Both cohorts were similar with respect to maternal immunosuppression, mode of delivery, and demographics. In summary, in a perinatal HIV observational study, the release of results of ACTG Protocol 076 was associated with an increase in zidovudine use during pregnancy and a concomitant decline in HIV transmission from mothers to infants.**

The rise in human immunodeficiency virus (HIV) infection among heterosexual women has been documented during the last decade, and in recent years, the rise has accounted for women experiencing the most rapid rate of increase in reported cases of AIDS of any group [1]. Concomitant with the rising incidence of infection among women of childbearing age has been an increasing number of children infected through perinatal transmission. Maternal-infant transmission, which varies between 15% and 40%, has resulted in an estimated 2000 HIV-infected children being born each year in the United States through 1993 [2, 3].

On 21 February 1994, the AIDS Clinical Trial Group (ACTG) announced preliminary results from their Protocol 076, a randomized, double-blind clinical trial of zidovudine to prevent HIV transmission from pregnant women to their infants [4]. This study enrolled 477 women by December 1993. The experimental regimen included oral antepartum zidovudine begun after the first trimester and intravenous zidovudine by constant infusion during labor and delivery, followed by the oral administration of zidovudine to the newborn for the first 6 weeks of life. On the basis of the 67.5% reduction in the risk of vertical transmission seen at the time of the first interim analysis, the study was halted, and the results released [5].

Because eligible participants in ACTG 076 were relatively asymptomatic and zidovudine naive and had >200/$\mu$L CD4 T lymphocytes at time of entry, it remained unclear how effective this regimen would be for the general population of HIV-infected pregnant women [6]. In addition, there continued to be concern that the use of zidovudine during pregnancy might increase the incidence of zidovudine-resistant HIV [7]. A task force was convened shortly after the results of this trial were released, and in July 1995, the US Public Health Service issued recommendations for HIV counseling and voluntary testing of all pregnant women, which stated that all HIV-infected pregnant women should be offered zidovudine after the first trimester of pregnancy [8]. Studies comparing the efficacy of zidovudine either alone or in conjunction with other interventions were planned and are currently underway in the United States. These studies include HIV-infected women with more advanced disease [9].

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Informed consent was obtained from all participants. The guidelines of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and requirements of the Title 45 code of Federal Regulations, part 46, Protection of Human Subjects, as well as the regulations of the authors' institutions were followed.

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The aim of this study was to investigate the impact of the release of ACTG Protocol 076 results by identifying temporal changes in the clinical pattern of zidovudine use during pregnancy and to evaluate the concomitant vertical transmission rate in the Women and Infants Transmission Study (WITS).

## Materials and Methods

WITS, an observational natural history study, has prospectively enrolled HIV-infected pregnant women since 1989. The women are followed with their infants through the infants' first few years of life. Participants are followed in New York, Boston, Chicago, Houston, and Puerto Rico. Data collected at study visits before 1 June 1995 were included in this analysis.

Peripheral blood mononuclear cells (PBMC) for HIV culture were obtained from infants during the first week of life, at 1, 2, 4, 6, 9, 12, 15, and 18 months, and every 6 months thereafter. All HIV cultures were done in ACTG-certified laboratories using the ACTG consensus protocol [10]. The WITS working definition of HIV infection requires 2 PBMC cultures positive for HIV. The time to diagnosis is defined as the time to the first positive culture. A child is classified as uninfected if there are no positive cultures and $\geq$2 negative cultures, with at least 1 being at $\geq$1 month of age and 1 at $\geq$6 months of age [11].

We considered the most recently enrolled singleton birth for each enrolled mother to form a mother-infant pair for this analysis. This maximized the number of cases in the period following 1 March 1994 while avoiding statistical problems due to correlated observations from multiple infants from the same mother. Of 796 mother-infant pairs meeting these criteria, 58 were coenrolled in ACTG 076 and were excluded from analysis. Of the remaining pairs, 144 infants had <6 months of follow-up as of 1 June 1995 and were excluded from those parts of the analyses that required infection status to be uniformly determined.

For purposes of investigating temporal changes in the transmission rate, the primary comparison groups were infants born on or before 1 March 1994 and those born after 1 March 1994. By this date, the results of ACTG 076 had been widely publicized and individual clinical centers had sufficient time to respond to the information and implement changes in clinic policy [12]. To minimize the bias due to differences in the amount of follow-up time in the cohort born on or before 1 March and that born after 1 March, only the first 12 months of culture data were considered when defining infection status. Most of the analysis is based on comparisons of the proportion infected, excluding cases with indeterminate infection status. In addition, a Kaplan-Meier analysis utilizing the entire cohort was used to estimate probability over time of being classified as infected.

Women enrolled in the cohort on or before 1 March 1994 were compared with those enrolled after this date, and separate transmission rates were calculated for variables thought to be associated with vertical transmission. These include degree of immunosuppression (as measured by percent CD4 lymphocytes), mode of delivery, gestational age, duration of membrane rupture, maternal viremia, and maternal illicit drug use [3, 13–15]. Drug use at any time during pregnancy was determined by a combination of self-report and urine toxicology analysis; reportable drugs included methadone, cocaine, heroin, opiates, and any injectable drugs.

To determine changes, if any, in the characteristics of the women enrolled in the WITS cohort after the results of ACTG 076 were released publicly, the 2 groups were compared with regard to the risk factors listed above as well as demographic information, including age, race, ethnicity, and trimester of pregnancy at the time of enrollment [16].

## Results

Compared with the interval immediately before 1 March 1994, the use of zidovudine during pregnancy in the WITS cohort rose from 22% to 70%, 90%, and 100% for women who delivered during the first 3 months, second 3 months, and $\geq$6 months after 1 March, respectively. Overall, 89% of women delivering after 1 March used zidovudine. There was a concomitant increase in the neonatal use of zidovudine, rising from 1% to 79%. Maternal-infant transmission rates were calculated for each year of the study for the 453 infants born on or before 1 March and compared by simple proportion method to the transmission rate for 103 infants born after 1 March who were

**Table 1.** Perinatal HIV transmission rates by characteristics of mothers giving birth on or before or after 1 March 1994.

| | Delivery on or before 1 March | | Delivery after 1 March | |
|---|---|---|---|---|
| Zidovudine use during pregnancy | | | | |
| Yes | 96 (22) | 15.6 | 91 (89) | 7.7 |
| No | 347 (78) | 20.0 | 11 (11) | 9.0 |
| % CD4 cells during pregnancy, mean | | | | |
| <29 | 229 (53) | 23.6 | 61 (60) | 8.2 |
| $\geq$29 | 207 (47) | 14.5 | 41 (40) | 7.3 |
| % CD8 cells during pregnancy, mean | | | | |
| <50 | 204 (47) | 15.2 | 43 (42) | 7.0 |
| $\geq$50 | 232 (53) | 22.8 | 59 (58) | 8.5 |
| Maternal peripheral HIV culture at delivery | | | | |
| Positive | 288 (76) | 20.5 | 66 (73) | 7.6 |
| Negative | 91 (24) | 9.9 | 25 (27) | 8.0 |
| Duration of rupture of membranes, h | | | | |
| $\leq$4 | 204 (56) | 12.2 | 51 (73) | 3.9 |
| >4 | 158 (44) | 23.4 | 19 (27) | 15.8 |
| Mode of delivery | | | | |
| Caesarean | 70 (17) | 18.6 | 12 (14) | 8.3 |
| Vaginal | 332 (83) | 17.8 | 74 (86) | 8.1 |
| Gestational age, weeks | | | | |
| <37 | 93 (21) | 24.7 | 15 (15) | 6.7 |
| $\geq$37 | 358 (79) | 17.3 | 88 (85) | 8.0 |
| Illicit drug use during pregnancy | | | | |
| Yes | 211 (48) | 22.3 | 28 (27) | 7.1 |
| No | 233 (52) | 15.9 | 75 (73) | 8.0 |
| All women | 453 (100) | 19.2 | 103 (100) | 7.8 |

NOTE. Data are no. (%) % transmission. Subjects with missing values were excluded from corresponding sections of table.

≥6 months of age. Vertical transmission rates were fairly stable at 19% between 1989 and 1994. After 1 March 1994, the rate declined to 8% ($P = .005$, Fisher's exact test). Kaplan-Meier analysis revealed a similar decline (from 18% to 7%) in the proportion classified as infected by 12 months of age ($P = .007$, log-rank test).

The characteristics of the cohorts before and after 1 March 1994 were similar with respect to degree of maternal immunosuppression (as measured by mean percent CD4 and CD8 cells during pregnancy), incidence of maternal viremia, mode of delivery, trimester of pregnancy at time of enrollment, length of gestation, age, race, and ethnicity (table 1, some data not shown). After 1 March, however, there were fewer women with >4 h of membrane rupture, representing a decrease from 44% to 27% of the cohort. In addition, there was a decline in the enrollment of women who were identified as using illicit hard drugs in the more recent cohort (48% to 27%).

Transmission rates were calculated separately for each of these risk factors (table 1). Consistently, there was a decline in the transmission rate in the more recent cohort. It would seem, therefore, that the temporal decrease in transmission rate was not an artifact of confounding due to a decrease in the prevalence of these potential risk factors. Further analysis is shown in table 2. Transmission rates were calculated for before and after 1 March 1994 and stratified by individual risk factors and zidovudine use. Although there is limited statistical power due to the small numbers in each category, there was a clear trend to lower transmission rates when zidovudine was used for each of the risk factors identified.

Prior to the release of the results of ACTG Protocol 076, 96 women in this analysis had received zidovudine during their pregnancy. This represented 22% of the cohort who gave birth on or before 1 March 1994. The vertical transmission rate in this group (16%) was not significantly different from that of their non–zidovudine-using counterparts. However, these women were distinctly different from the cohort of zidovudine users after 1 March with regard to degree of immunosuppression (table 3). The percent CD4 cell levels of 29% and 14% correspond to absolute CD4 cell counts of 512 and 225, respectively, when applied to the WITS data. The women who received zidovudine during the earlier time period were more likely to have mean percent CD4 cell levels <14% during their pregnancy (21% vs. 12%) and less likely to have levels >29% (26% vs. 42%) compared with zidovudine users in the later time period. In addition, their use of zidovudine during pregnancy was less likely to be associated with intrapartum or neonatal administration. Their zidovudine use was discontinuous in many cases and includes only first trimester use in others.

**Table 2.** Perinatal HIV transmission rates by maternal risk factors and zidovudine use during pregnancy of women giving birth on or before or after 1 March 1994.

| | | Delivery on or before 1 March | | | Delivery after 1 March | | |
|---|---|---|---|---|---|---|---|
| | Zidovudine use | No. of infected mothers | No. of infected infants | % transmission | No. of infected mothers | No. of infected infants | % transmission |
| % CD4 cells during pregnancy, mean | | | | | | | |
| <14 | Yes | 20 | 4 | 20.0 | 11 | 1 | 9.1 |
| | No | 16 | 5 | 31.3 | 0 | 0 | — |
| 14–18 | Yes | 51 | 10 | 19.6 | 42 | 3 | 7.1 |
| | No | 139 | 35 | 25.2 | 8 | 1 | 12.5 |
| ≥29 | Yes | 25 | 1 | 4.0 | 38 | 3 | 7.9 |
| | No | 181 | 29 | 16.0 | 2 | 0 | 0.0 |
| % CD8 cells during pregnancy, mean | | | | | | | |
| <50 | Yes | 31 | 2 | 6.5 | 37 | 2 | 5.4 |
| | No | 172 | 29 | 16.9 | 5 | 1 | 20.0 |
| ≥50 | Yes | 65 | 13 | 20.0 | 54 | 5 | 9.3 |
| | No | 164 | 40 | 24.4 | 5 | 0 | 0.0 |
| Maternal peripheral HIV culture at delivery | | | | | | | |
| Positive | Yes | 72 | 12 | 16.7 | 57 | 4 | 7.0 |
| | No | 212 | 47 | 22.2 | 8 | 1 | 12.5 |
| Negative | Yes | 13 | 0 | 0.0 | 23 | 2 | 8.7 |
| | No | 78 | 9 | 11.5 | 2 | 0 | 0.0 |

NOTE. Subjects with missing values were excluded from corresponding sections of table. Only mothers with infants ≥6 months old were included.

**Table 3.** Characteristics of pregnant zidovudine users.

| | Delivery on or before 1 March 1994 | Delivery after 1 March 1994 |
|---|---|---|
| % CD4 cells during pregnancy, mean | | |
| <14 | 20 (20.8) | 11 (12.1) |
| 14–28 | 51 (53.1) | 42 (46.2) |
| ≥29 | 25 (26.0) | 38 (41.8) |
| Duration of ruptured membranes, h | | |
| ≤4 | 52 (64.2) | 44 (72.1) |
| >4 | 29 (35.8) | 17 (27.9) |
| Mode of delivery | | |
| Caesarean | 12 (13.5) | 11 (14.5) |
| Vaginal | 77 (86.5) | 65 (85.5) |
| Gestational age, weeks | | |
| <37 | 20 (20.8) | 11 (12.1) |
| ≥37 | 76 (79.2) | 80 (87.9) |
| Illicit drug use during pregnancy | | |
| Yes | 44 (45.8) | 25 (27.5) |
| No | 52 (54.2) | 66 (72.5) |

NOTE. Data are no. (%).

Only 2 mother-infant pairs received zidovudine before March 1994, representing only 0.5% of the entire cohort. After 1 March, 76% of the mother-infant pairs received at least part of the recommended zidovudine regimen.

We attempted to assess adherence to the ACTG 076 three-component regimen since the release of the new clinical guidelines. Complete data were available for 88 women whose infants were delivered after 1 March 1994. Of these, 66 (75%) had received the complete three-part regimen consisting of antepartum, intrapartum, and infant administration of zidovudine. Of the remaining 11 mother-infant pairs, 5 received only the antepartum component, 3 received antepartum and intrapartum components, 1 received only the infant component, and 2 did not receive any part of the preventive regimen.

## Discussion

The use of zidovudine has risen significantly in the WITS cohort since the results of ACTG 076 were first released in late February 1994, and the rate of vertical transmission in this cohort has decreased dramatically over the same time period. Thus, the findings of this study are consistent with those of the ACTG 076.

Duration of membrane rupture decreased in the cohort that gave birth after 1 March compared with the earlier time period and was associated with transmission within each time period (table 1). However, there was a temporal decline in transmission rates both for those with short and those with long duration. Thus, the changing pattern of duration of membrane rupture over time did not confound or explain the decline in the rate of vertical transmission. The importance of duration of membrane rupture in the WITS cohort has been explored in greater detail by Landesman et al. [17].

The decline in drug use among women enrolling in the cohort has been gradual throughout the WITS study and may reflect the changing epidemiology of the HIV epidemic in heterosexual women in the United States. The very small number of women who transmitted HIV to their infants after 1 March 1994 makes a more sophisticated multivariate analysis difficult; therefore, we cannot confirm in this observational study that the decrease in overall transmission is attributable to zidovudine alone.

The apparent relative lack of efficacy of isolated antepartum zidovudine in the cohort giving birth on or before March 1994 could suggest that the other components of the ACTG 076 regimen are more important to risk reduction. However, it is likely that most of the women in the cohort giving birth before 1 March were receiving zidovudine for clinical indications, such as their own disease progression, and may indeed have had a greater risk of vertical transmission than that of the general cohort. The transmission rate of 15.6% in this zidovudine-using group may represent a reduction from that which would have been documented without therapeutic intervention. To estimate the efficacy of zidovudine, therefore, it may not be fair to compare the vertical transmission rate in this cohort to the cohort giving birth after 1 March. Several studies have suggested that advanced immunosuppression is directly related to higher rates of transmission [14, 15]. The efficacy of zidovudine documented in our study is consistent with that found by Matheson et al. [16] in their population in New York City, which included women with advanced immunosuppression.

Because of the difficulty in collecting complete information regarding the use of intrapartum zidovudine and because of the small number of cohort infants born since March 1994 with documented infection, our data do not allow us to draw conclusions as to the individual roles of antenatal, intrapartum, and infant use of zidovudine in the prevention of vertically transmitted HIV. It will be important to determine if the efficacy of each individual component of the treatment regimen varies with stage or individual characteristics of maternal disease. Both of these questions will probably require large cooperative studies. One approach might include pooling of data across several large observational studies. Other research approaches may come from clinical trials in developing countries designed specifically to evaluate the efficacy of compressed 076 regimens.

In summary, within a large perinatal HIV observational study, release of the ACTG 076 results was temporally associated with an increase in the use of zidovudine during pregnancy and with a decrease in maternal-infant HIV transmission. This study is consistent with the findings of the landmark study, and emphasizes the need for future investigations designed to address prevention of perinatal HIV infection in those women who may be at highest risk. Our experience underscores that clinical trial results must be quickly translated into "real-

world'' settings. In combination with other studies, our results support the recent US Public Health Service guidelines recommending that zidovudine use be discussed and offered to all HIV-seropositive pregnant women. This argues the importance of universal prenatal HIV counseling with voluntary testing in order that appropriate preventive interventions be offered. While some have suggested that mandatory screening of pregnant women for HIV may be beneficial in light of the ACTG 076 results [18], most agree that voluntary prenatal testing after counseling is preferable, since successful interventions will require the full understanding and cooperation of the expectant mother.

In our society, the negative social consequences of being identified as HIV-infected often make preventive strategies difficult to incorporate into routine clinical care [19]. Our study demonstrates that with adequate counseling, most HIV-infected women in the WITS cohort opted to receive the 076 regimen. We must continue to investigate strategies to approach the problem of HIV vertical transmission from the scientific and medical perspectives, always mindful of the social ramifications.

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