Addition of Single-Dose Tenofovir and Emtricitabine to Intrapartum Nevirapine to Reduce Perinatal HIV Transmission

Benjamin H. Chi, MD, MSc,*† Namwinga Chintu, MBChB, MMed, MTrop,* Ronald A. Cantrell, MPH,** Chipepo Kankasa, MD, MMed,‡ Gina Kruse, MSc,* Felistas Mbewe, RN, BSc,* Moses Sinkala, MBChB, MPH,†§ Peter J. Smith, PhD, k Elizabeth M. Stringer, MD, MSc,*† and Jeffrey S. A. Stringer, MD*†

Objective: To determine the impact of adjuvant single-dose peripartum tenofovir/emtricitabine (TDF/FTC) on intrapartum/early postpartum HIV transmission.

Methods: In the setting of routine short-course zidovudine (ZDV) and peripartum nevirapine (NVP) for perinatal HIV prevention, participants were randomized to single-dose TDF (300 mg)/FTC (200 mg) or to no intervention in labor. Six-week infant HIV infection was compared according to actual-use drug regimens.

Results: Of 397 women randomized, 355 (89%) had infants who were alive and active at 6 weeks postpartum. Of these, 18 (5.1%) were infected in utero and 6 (1.8%) were infected intrapartum/early postpartum. Among the 243 who used ZDV and NVP, intrapartum/early postpartum transmission was not reduced among infants whose mothers received TDF/FTC compared with those who did not (2 of 123 [1.6%] vs. 3 of 109 [2.8%]; \( P = 0.67 \)). Among the 49 infants whose mothers did not receive antenatal ZDV but who had confirmed NVP ingestion, transmission similarly did not differ (0 of 19 [0%] vs. 1 of 26 [3.4%]). TDF/FTC was not significantly associated with reduced overall transmission (odds ratio [OR] = 0.7, 95% confidence interval [CI]: 0.3 to 1.6), even when other antiretroviral drugs were considered (adjusted OR = 0.8, 95% CI: 0.3 to 1.8).

Conclusions: Adjuvant peripartum single-dose TDF/FTC did not reduce perinatal transmission. Whether a higher dose might be effective remains unknown but should be studied in settings in which NVP is used without antenatal ZDV.

Key Words: emtricitabine, HIV, nevirapine, perinatal HIV prevention, tenofovir, Zambia

Despite worldwide expansion of programs to prevent mother-to-child HIV transmission, as many as 1000 infants still become infected with the virus each day. Combination antiretroviral drug regimens can virtually eliminate perinatal HIV transmission but are impractical for routine use in many resource-constrained settings. As a result, a priority has been placed on identifying efficacious yet simple prophylactic regimens. Because of their long half-lives and demonstrated tolerability, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) have been proposed as candidate drugs for perinatal HIV prevention.

We performed a randomized trial of intrapartum TDF/FTC to reduce nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in the setting of single-dose intrapartum and neonatal nevirapine (NVP). A secondary outcome of the study protocol was perinatal HIV transmission. When we analyzed the data according to study arm allocation, difference in transmission between control (8.0%) and intervention (5.6%) arms did not reach statistical significance \( (P = 0.40) \). In this report, we further explore the impact of adjuvant TDF/FTC on perinatal HIV transmission using actual-use data.

METHODS

We conducted a randomized trial at 2 public health clinics in Lusaka, Zambia. The methods have been described elsewhere. Briefly, HIV-infected pregnant women were identified and enrolled into the study between 28 and 38 weeks of completed gestation. We excluded women who had previously used antiretroviral drugs and those who qualified for antiretroviral therapy (ART) based on World Health Organization criteria. Random allocation to study arms was performed on arrival to the study facility in labor. Participant mothers and their babies were followed up at 2 weeks and 6 weeks postpartum. Newborn and infant dried blood spots were collected at birth and at 6 weeks of life, respectively, and were
tested for HIV DNA with the Roche Amplicor HIV-1 DNA Test Version 1.5 (Roche Molecular Systems, Branchburg, NJ). Two consecutive positive DNA polymerase chain reaction (PCR) tests were required for diagnosis of HIV. Transmission was considered intrauterine if the birth and 6-week results were both positive and intrapartum/early postpartum if the baby tested HIV-negative at birth but positive at 6 weeks.8

As part of the routine antenatal care at the study sites, all women who did not immediately qualify for ART were offered zidovudine (ZDV) from 32 weeks of gestation onward and intrapartum NVP.9 All HIV-exposed newborns were given a 2-mg/kg dose of NVP syrup before discharge, and their mothers were provided with a week-long supply of ZDV syrup to be administered at 4 mg/kg twice daily. To assess uptake of and adherence to antenatal ZDV, we collected pharmacy refill information. We then calculated the participant’s medication possession ratio (MPR),10 a measure of adherence that describes the proportion of days the participant had ZDV on hand from drug initiation to delivery. Because of high rates of NVP nonadherence reported in previous studies,11 we analyzed cord plasma to verify ingestion of the drug. We used a previously published methodology for NVP detection by means of high-performance liquid chromatography.12 The lower limit of quantification was set at 0.01 µg/mL. Participants randomized to the intervention arm were administered TDF (300 mg) and FTC (200 mg) in a combination dose under direct observation.

We analyzed categorical variables using the Fisher exact test. Two-tailed t tests were used for normally distributed continuous variables, and Wilcoxon rank sum tests were used to compare parameter medians when distribution was not believed to be normal. Odds ratios were used to estimate relative risk. To determine the independent contribution of each antiretroviral drug component (ie, short-course ZDV, intrapartum NVP, intrapartum TDF/FTC) on perinatal HIV transmission, we built logistic regression models. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). The study was approved by the University of Zambia Research Ethics Committee (Lusaka, Zambia) and the University of Alabama at Birmingham Institutional Review Board (Birmingham, AL).

RESULTS

We randomized 397 women between March 16, 2005 and February 13, 2007. Three women (1%) delivered a stillborn baby, and 9 (2%) had babies who were born alive but died before 6 weeks of life. Between birth and 6 weeks, 30 (8%) mother-child pairs were lost to follow-up. HIV transmission data were thus available for 355 (89%) mother-infant pairs.

Of the 355 mother-infant pairs included in this analysis, 180 (51%) were allocated to the intervention arm and 175 (49%) were allocated to the control arm. NVP was detectable in infant cord blood among 292 (82%) of 355 women, a figure similar to previous studies in Lusaka.11,13 ZDV use in the antenatal period was confirmed by means of pharmacy records in 294 (83%) of 355 women. Among them, median gestational age at initiation was 33.0 weeks; average duration from initiation until delivery was 36.8 days. By the MPR metric, 159 (54%) of 294 demonstrated perfect adherence.

Overall, 24 (7%) of 355 infants were infected with HIV by 6 weeks of life. Of these cases, most occurred during the intrauterine period (n = 18) when compared with the intrapartum/early postpartum period (n = 6). As previously reported,4 transmission rates were similar between intervention and control arms for intrauterine (4% vs. 6%; P = 0.63), intrapartum/early postpartum (1% vs. 2%; P = 0.44), or overall (6% vs. 8%; P = 0.40) transmission. When compared with nontransmitting mother-infant pairs, transmitting pairs had lower mean maternal CD4 counts at baseline (379 cells/µL [SD = 106] vs. 485 cells/µL [SD = 208]; P < 0.001), had a shorter mean duration of ZDV prophylaxis (25 days [SD = 18] vs. 38 days [SD = 24]; P = 0.03), and were less likely to have viral load <400 copies/mL immediately after delivery (5% vs. 31%; P < 0.01). Women who transmitted HIV to their babies also started antenatal ZDV later in pregnancy (median: 35 vs. 33 weeks; P = 0.05). No differences were noted among other demographic, medical, and delivery characteristics (Table 1).

Among 243 participants with confirmed ZDV and NVP use, addition of TDF/FTC was not associated with statistically different rates of intrapartum/early postpartum (2 of 123 [1.6%] vs. 3 of 109 [2.8%]; P = 0.67) or overall (5 of 126 [4.0%] vs. 11 of 117 [9.4%]; P = 0.12) HIV transmission. Similarly, among the 49 infants whose mothers did not use antenatal ZDV—but in whose cord plasma, we detected NVP—the addition of intrapartum TDF/FTC did not significantly reduce transmission in the intrapartum/early postpartum period (0 of 19 [0%] vs. 1 of 26 [3.4%]) or overall (3 of 22 [13.6%] vs. 2 of 27 [7.4%]; P = 0.65) (Table 2). Perinatal HIV transmission observed with other antiretroviral drug regimens is shown in Table 2, including 7 women with missing NVP cord plasma data. In an unadjusted model, intrapartum TDF/FTC was not associated with a statistically significant reduced risk for overall HIV transmission (odds ratio = 0.7, 95% confidence interval: 0.3 to 1.6). This result was virtually unchanged when we considered concomitant use of ZDV or NVP in multivariable analysis (Table 3).

DISCUSSION

In this secondary analysis, we used measures of adherence and study arm allocation to compare the relative efficacy of different antiretroviral drug regimens for perinatal HIV prevention. We observed a trend toward reduced HIV transmission when TDF/FTC was added to a regimen of antenatal ZDV and intrapartum NVP in unadjusted analysis. In multivariable models, however, there was not an independent protective effect associated with TDF/FTC.

As recommended by the World Health Organization, all participants in this trial were first screened for ART eligibility. Those who met local criteria for treatment were excluded from consideration; those who did not were offered antenatal ZDV and periartum NVP and were approached about the study.13 In this setting, overall intrapartum/early postpartum transmission was <2%. An adjuvant intervention to NVP—even if shown to be effective—would likely have low incremental benefit.
Our results suggest that when the infrastructure for anti-retroviral drug distribution is available, efforts should focus on improved antenatal HIV prophylaxis. Earlier access to ZDV during pregnancy or use of more efficacious combination regimens could have reduced HIV transmission in our study setting, because three quarters of these cases occurred during the intrauterine period.

In settings in which antenatal ZDV is not used and single-dose NVP is the standard of care, it is possible that an adjuvant intrapartum intervention such as TDF/FTC may hold promise, because HIV transmission around the time of birth is more likely. Work in Lusaka, for example, reported a 9% intrapartum/early postpartum transmission rate when NVP was used alone. Similar results (8%) were demonstrated in...
TDF/FTC use during labor

NVP use during labor

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REFERENCES


