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Chlamydia and Gonorrhea in HIV-infected Pregnant Women and Infant HIV Transmission

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Abstract

BACKGROUND—Sexually transmitted infections (STIs) such as *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) can lead to adverse pregnancy and neonatal outcomes. STI prevalence and its association with HIV mother-to-child transmission (MTCT) were evaluated in a sub-study analysis from a randomized, multi-center clinical trial.

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METHODOLOGY—Urine samples from HIV-infected pregnant women collected at the time of labor and delivery were tested using polymerase chain reaction (PCR) testing for the detection of CT and NG (Xpert® CT/NG, Cepheid, Sunnyvale, CA). Infant HIV infection was determined by HIV DNA PCR at 3 months.

RESULTS—Of the 1373 urine specimens, 249 (18.1%) were positive for CT and 63 (4.6%) for NG; 35 (2.5%) had both CT and NG detected. Among 117 cases of HIV MTCT (8.5% transmission) the lowest transmission rate occurred among infants born to CT and NG uninfected mothers (8.1%) as compared to those infected with only CT (10.7%) and both CT and NG (14.3%), (p = 0.04). Infants born to CT-infected mothers had almost a 1.5-fold increased risk for HIV acquisition (OR 1.47, 95% CI 0.9–2.3, p=0.09).

CONCLUSION—This cohort of HIV-infected pregnant women are at high risk for infection with CT and NG. Analysis suggests that STIs may predispose to an increased HIV MTCT risk in this high risk cohort of HIV-infected women.

Keywords

maternal to child transmission; HIV; pregnancy; chlamydia; gonorrhea; sexually transmitted infections

INTRODUCTION

Sexually transmitted infections (STIs) including *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) pose a tremendous burden worldwide. In 2008, the World Health Organization (WHO) estimated that 105.7 million new CT and 106.1 million NG infections occurred.(1) STIs remain highest in low and middle-income countries, including in regions of Africa and Latin America. HIV-infected pregnant women represent a high-risk, neglected group for STIs.

Untreated chlamydial and gonococcal infections can have serious consequences in pregnant women. They may lead to fetal loss, premature rupture of membranes, and preterm labor and delivery.(2–5) Maternal chlamydial infections may lead to conjunctivitis and pneumonia in infants.(4) Gonococcal infections may also cause neonatal conjunctivitis and in rare cases can lead to disseminated infections in infants.(3)

In addition, STIs such as CT and NG have been postulated to increase the risk of human immunodeficiency virus (HIV) transmission from mother-to-child. Studies from non-pregnant women suggest those STIs may increase genital HIV viral shedding, which may be attenuated by STI treatment.(6) (7) Other research has focused on a role for STIs in increasing HIV mother-to-child transmission (MTCT), particularly *in-utero* transmission, by triggering placental inflammation or chorioamnionitis.(8–15) However, few studies have provided direct support of causality, especially for CT and NG.(16–19)

Given limited published research documenting the prevalence of CT and NG in HIV-infected pregnant women in low and middle-income countries and the potential impact of these infections on HIV MTCT, the following sub-study evaluated rates of CT and NG infection in a high risk group of HIV-infected mothers. We characterized rates of CT and

NG infection by geographic distribution, socio-demographics, pregnancy, and HIV-related maternal parameters. We also wanted to determine if maternal CT and NG infection was associated with increased HIV MTCT.

METHODS

Study Design

This study was a sub-study of the National Institute of Child Health and Human Development (NICHD) HIV Prevention Trials Network (HPTN) 040 trial. NICHD/HPTN 040 (P1043) was a phase 3, triple-arm, randomized, open-label, multi-center study aimed at the prevention of *intrapartum* HIV transmission to infants born to HIV-infected pregnant women, who had not received antiretrovirals drugs until labor and delivery due to late diagnosis of infection. The study evaluated the efficacy, safety, and tolerance of three different infant antiretroviral prophylaxis regimens. The study demonstrated that infants receiving 2 or 3-drug antiretroviral HIV prophylaxis had a decreased risk of acquiring *intrapartum* HIV-infection than zidovudine alone. (20) Subjects were enrolled between April 2004 to July 2010.

Study enrollment consisted of 1684 HIV-infected pregnant women diagnosed as HIV-infected at the time of labor and delivery. All mothers provided written informed consent. Enrollment occurred at multiple sites in Brazil, South Africa, Argentina, and the United States. Infants <32 weeks of age were excluded from the study.

At the time of enrollment, all mothers were interviewed about risk behaviors including use of illegal substances, alcohol, and tobacco during pregnancy. Data were collected on history of prior STIs and STI symptoms but were unable to be analyzed due to insufficient number of responses. Information was obtained regarding receipt of prior prenatal care and obstetric history including prior preterm deliveries and stillbirths. Maternal plasma HIV RNA levels and T lymphocyte subsets were obtained at the time of labor and delivery. Additionally, syphilis testing was performed at the time of labor and delivery using Venereal Disease Research Laboratory (VDRL) test titers with confirmatory treponemal syphilis antibody tests, as per standard of care.(48) Infant data from the time of birth were collected, including HIV antiretroviral treatment arm. Infants were followed until 6 months of age for safety and toxicity monitoring in the parent study. The primary endpoint of the parent study was HIV infection status at 3 months of age.

HIV Diagnosis

HIV testing of infants occurred within 48 hours of birth, 14 days, 4–6 weeks, 3, and 6 months of age. Confirmatory HIV DNA testing was done for positive results. Diagnosis of infant HIV infection required two positive HIV DNA polymerase chain reaction (PCR) (Roche Molecular Systems Inc., Basel, Switzerland) results collected on different days. During the primary study, infants with a positive HIV DNA PCR test result at birth and confirmatory results on repeat testing were classified as having *in utero* HIV infection. Infants with a negative HIV DNA PCR result at birth and positive results on subsequent testing were classified as *intrapartum* HIV infection. HIV laboratory assays were performed

by quality assured laboratories supported by the NICHD and the International Maternal Pediatric Adolescent AIDS Clinical Trials group. All HIV-exposed infants enrolled in the study were formula fed.

Specimen Collection and Chlamydia and Gonorrhea Testing

Stored maternal urine samples collected at the time of labor and delivery or within 48 hours of giving birth were frozen and stored at study sites. Aliquots (7 mL each) of stored frozen urine were shipped for testing at Cepheid, Sunnyvale, CA. Urines were tested for the presence of CT and NG using the Xpert® CT/NG assay. Results were reported as positive, negative or indeterminate. Indeterminate test results were repeated up to two times, and those that remained indeterminate were excluded from data analysis.

Statistical Analysis

The Kruskal-Wallis test was used to compare the median differences for continuous variables (age in years, CD4 count, and log10 HIV viral load) with respect to categorical outcome (STI status: CT only, NG only, CT and NG co-infection, and uninfected). Chi-square test was used to compare differences in STI prevalence for categorical variables. Univariate and multivariable logistic regression modeling was then used to examine the relationship of overall maternal STI status with demographic, substance use, pregnancy, and select characteristics including study site, categorical age, occupation, race/ethnicity, illegal substance use, alcohol use, tobacco use, prior preterm birth, prior stillbirth, prenatal care status, and mode of delivery. In order to further assess the association of potential risk factors with each STI group, stratified analyses were also performed. The covariates with a p-value of 0.2 or less were selected to enter into the initial model selection. Covariates with an overall p-value less than 0.05 were retained in the final model. To compare STI groups with respect to HIV MTCT as a categorical outcome, frequency distributions were done and p-values were calculated with the exact test from Monte Carlo simulations. Odds ratio using 95% confidence interval (CI) and p-values were calculated from exact logistic models to further evaluate the relationship between maternal STI groups and the outcome of HIV MTCT. All computations were done using SAS software v9.3 (Cary, NC, USA).

Human Subjects

Both the parent trial and the sub-study were approved by the relevant institutional review boards.

RESULTS

Urine samples from 1406 HIV-1-infected women were tested using the Xpert® CT/NG assay on the GeneXpert platform. After the exclusion of 33 invalid or inconclusive results, data from participants with 1373 valid urine test results were included in the analysis (81.5% of the 1684 women enrolled in the parent study).

Chlamydia and Gonorrhea Prevalence

Of the 1373 HIV-infected pregnant women included in this study, 249 (18.1%) had CT, 63 (4.6%) had NG, and 35 (2.5%) were co-infected with both CT and NG. Overall, 277

(20.2%) of this sample were positive for CT, NG, or both CT and NG. Rates of CT and NG were highest in South Africa, where 21.3% (87) had CT and 7.6% (31) had NG. Rates were also high in Brazil, where 17.1% (160) were positive for CT and 3.4% (32) were positive for NG. In Argentina, there were no cases of NG, but CT was identified among 10.5% (2) of the 19 women. No cases of either CT or NG were found among the seven women enrolled in the U.S.

Chlamydia, Gonorrhea, and Association with Maternal Parameters

Of the 1373 HIV-infected pregnant women included in this analysis, 938 (68.3%), 409 (29.8%), 19 (1.4%), and 7 (0.5%) women were enrolled from study sites in Brazil, South Africa, Argentina, and the U.S, respectively. This distribution is commensurate with the distribution of subjects in the main study. The overall mean age of women at all study sites was 26.9 years (standard deviation 6.4). Table 1 shows various study participant characteristics by STI status. Significant differences were noted by age ($p<0.0001$). Women between 13 to 24 or 25 to 29 years of age were 2.2 times (OR 2.2, 95% CI 1.6–3.1) or 1.7 times (OR 1.7, 95% CI 1.1–2.4) more likely to have an STI (CT, NG, or both) than those 30 years or over. Additional analysis revealed that younger age (13 to 24 years) was also specifically associated with any CT, NG, or co-infection. That association was most pronounced for younger women and CT and NG co-infection (OR 6.2, 95% CI, 2.1–18.3). (Tables 1, 2, 3)

High rates of illegal substance, tobacco, and alcohol usage in pregnancy were found in the sample: 111 (8.1%) women reported use of illegal substances, while 438 (32.1%) used tobacco and 476 (35%) used alcohol during pregnancy. Significant differences in usage by STI group were noted for illegal substance ($p=0.05$) and tobacco use ($p=0.02$). Illegal substance usage was associated with NG infection and co-infection in the initial unadjusted analysis. Only tobacco usage was significantly associated with overall STI (OR 1.4, 95% CI 1.1–1.9) as well as any CT (OR 1.4, 95% CI 1.0–1.8) or NG infection (OR 1.8, 95% CI 1.1–3.1) by adjusted logistic regression analyses. (Tables 1, 2, 3)

Of the study sample, 845 (61.7%) women reported at least some prenatal care during their pregnancy with significant differences noted by STI status ($p < 0.001$). Receiving prenatal care in pregnancy was protective against any STI (OR 0.7, 95% CI 0.6–0.98) with similar findings noted for adjusted analysis for any CT (OR 0.7, 95% CI 0.5–0.96), NG (OR 0.5, 95% CI 0.3–0.9), or CT and NG co-infection (OR 0.3, 95% CI 0.2–0.7). Women who were delivered by cesarean-section were less likely to have an STI (OR 0.5, 95% CI 0.3–0.6) with similar findings also noted when evaluated specifically for any CT, NG, or co-infection. (Tables 1, 2, 3)

Women also reported high rates of prior adverse pregnancy and neonatal outcomes: 252 (18.5%) women reported a history of prior preterm birth with significant differences found by STI group, and 59 (4.3%) reported a history of prior stillbirth. While prior preterm birth was associated with any STI as well as any NG or CT and NG co-infection in unadjusted analyses, these were not significant findings with adjusted analyses. Prior history of stillbirth was associated with any STI and CT infection in preliminary evaluation but was not significant after adjusted analyses. (Tables 1, 2, 3)

The median maternal CD4 count at delivery was 458 (interquartile range (IQR) 291–663) cells/mm3, and the median log10 HIV plasma viral load was 4.2 (IQR 3.6–4.7) copies/mL. No significant differences were noted by STI status. No associations were found between CD4 count or log10 HIV plasma viral load and overall STI status, CT, NG, or CT and NG co-infection. Viral load was also dichotomized using cutoffs of >20,000 as well as >25,000 copies/mL but continued to show no significant difference in the number of women with higher viral loads (>20,000 or >25,000) among STI groups (Table 1–2)

Chlamydia, Gonorrhea, and HIV Mother-to-Child Transmission

There were 117 cases (8.5% transmission) of HIV MTCT in our study sample, of which 75 cases (64.1%) occurred *in utero* and 42 cases (35.9%) *intrapartum*. HIV MTCT rates were lowest among infants born to CT and NG uninfected mothers as compared to those infected with CT only or both CT and NG (8.1% versus 10.7% and 14.3% respectively, (p =.04). There were no cases of HIV MTCT among NG-infected mothers. *In utero* HIV MTCT was the highest among mothers co-infected with CT and NG (8.6%) or mothers who had CT alone (7.5%). In contrast, HIV MTCT rates in women without an STI were 5.1% for *in utero* transmission and 3.0% for *intrapartum* HIV transmission. A marginally statistically significant association between CT-infected mothers and overall HIV MTCT was noted by logistic regression analysis (OR 1.47, 95% CI 0.9–2.3) with similar findings for *in utero* HIV MTCT (OR 1.59, 95% CI 0.9–2.7). Comparisons of HIV MTCT among women dually infected with CT and NG and those without these STIs demonstrated a 6.2% difference in HIV MTCT rates, although results were not statistically significant. (Tables 4–5). In this sub-cohort, 129 women were VDRL positive (9.4%), a similar rate to that reported in the parent study of 10%. (20) Twenty-nine women with syphilis (22.5% of the VDRL positive women in this cohort) were also co-infected with CT, NG or both. In this group there were 5 transmissions, 4 in utero and 1 intrapartum, An analysis of syphilis co-infection in the 040 study has been recently published. (48)

DISCUSSION

Prevalence of Chlamydia and Gonorrhea and Maternal Parameters

This study is notable for the high prevalence of CT (18.1%) and NG (4.6%) among a unique cohort of HIV-infected pregnant women with a late diagnosis of HIV and a possible association of CT infection with increased HIV MTCT. Limited published data exists on the prevalence of CT and NG in pregnant women in Latin America and Africa. Prior WHO estimates of CT and NG infections among women may underestimate the prevalence of these infections, particularly as they are often asymptomatic. For instance, WHO prevalence estimates of CT and NG are 2.6% and 2.3% among women in Africa, and 7.6% for CT and 0.8% for NG in the Americas.(1)

Our analysis of STI prevalence by country study site revealed that STI rates in this high risk group of HIV-infected pregnant women were particularly elevated in South Africa (CT 21.3%, NG 7.6%) and in Brazil (CT 17.1%, NG 3.4%). Our sample's STI rates appear higher than most reported studies from Brazil, Argentina, and African countries. (11) (18) (21–25)

Our results that younger maternal age and a history of no prenatal care were associated with CT or NG infection have also been documented in prior studies. (17) (26–28) Lack of prenatal care and STIs has also been previously reported, especially with regards to higher rates of HIV and other STIs such as syphilis.(29) In our study, although over half of the sample had some form of prenatal care, it was clear that prenatal care had been suboptimal as mothers were only found to be HIV-infected at the time of delivery. Tobacco usage has also been associated as a risk factor for STIs, CT in particular, in prior studies.(30) (31) Although our study found high rates of substance use, adjusted analysis failed to confirm association with STIs such as NG. None of the women reported being sex workers, although information regarding exchange of sex for drugs or money was not collected.

Women in our sample also had high rates of prior adverse pregnancy outcomes. Over 18% reported a history of prior preterm birth, which is much higher than preterm birth rates reported in the general populations in the U.S. (12%), Brazil (9.2%), and South Africa (8%). (32) Similarly, the prior stillbirth rate of 4.3% in our study population appears to be high, although it has been reported to range from 3.1 to 32.9 per 1000 total births in some high income countries and in sub-Saharan Africa.(33) (34) While differences in prior history of preterm birth and STI group were noted, no significant association was found after adjusted analysis. That initial association in the unadjusted analysis was interesting because STIs are a known risk factor for preterm birth.(3) (35–37)

HIV Mother-to-Child Transmission

The collective results of this study appear to provide some support for the hypothesis that maternal STIs (CT and possibly CT in combination with NG) in pregnancy may predispose to an increased risk of HIV MTCT, particularly *in utero* transmission. However, the relationship was not noted for NG only-infected women, where there were no cases of HIV MTCT. One explanation for this lack of association for maternal NG-infection and HIV MTCT may be due to the small number of NG-only infected women, but should be interpreted cautiously. In addition, the ability to observe any effect of maternal STIs on *intrapartum* transmission may have been limited by the parent study's objective of evaluating antiretroviral prophylaxis regimens to prevent *intrapartum* HIV transmission. As the interventions were effective in preventing intrapartum HIV acquisition, a much smaller number of *intrapartum* infections occurred.

Overall, our findings appear consistent with one of the primary studies to find a positive association between STIs such as CT or NG and increased risk of HIV MTCT, which was a randomized controlled trial of 1078 HIV-infected pregnant women evaluating the role of vitamin supplements and HIV MTCT.(16) Although NG infection in the study population was only 1% and those infected were treated, they found NG-infected mothers had a 5.5-fold increased risk for intrauterine HIV transmission; CT was not part of their evaluation. (16) However, our findings contrast with other studies including one from Thailand that did not show increased HIV MTCT in spite of high STI rates, and the Rakai, Uganda STI treatment intervention study that failed to decrease HIV MTCT in spite of lowering rates of STIs among pregnant women.(17–19) (38) Another phase 3 clinical trial in sub-Saharan Africa (HPTN 024) also did not show improvement in either HIV MTCT or pathological

chorioamnionitis with antenatal and intrapartum antibiotics given to reduce rates of chorioamnionitis from other genital tract infections such as bacterial vaginosis and *Trichomonas vaginalis*.(9) (11) (39) Maternal plasma viral load is considered one of the main predictors of HIV MTCT even though our study found no differences in maternal plasma HIV viral load by STI group even when stratified by those with viral loads >20,000 or >25,000 copies/mL, which may pose higher risks of MTCT. Other commonly cited MTCT risk factors include low CD4 counts, increased exposure to maternal blood or cervicovaginal secretions, and chorioamnionitis. (12) (16) (40) Maternal plasma viral load was not significantly different in mothers co-infected with STIs in comparsion to those uninfected with STIs. The role of STIs as a risk factor for increased HIV MTCT has been suggested by observational studies in pregnant women with genital tract infections including herpes simplex virus-2, bacterial vaginosis, human papilloma virus, and syphilis.(13) Multiple studies in non-pregnant women have suggested that STIs including CT and NG may increase the risk of HIV cervicovaginal viral shedding possibly from inflammation-induced recruitment of HIV-infected cells in secretions, T-cell activation resulting in increased replication of HIV, and disruption of the mucosal epithelial barrier.(6) (7) (41) (42) Increased HIV shedding is estimated to range by as much as 1.5–1.8-fold for CT and 1.8–2.4-fold for NG, (41) (42) but may be reduced by STI treatment.(6) (7)

Apart from genital tract infections triggering cervicitis, which may increase HIV MTCT via enhanced cervicovaginal HIV viral shedding, (13) (43) (44) some studies suggest STIs may also play a role in increased HIV MTCT by causing chorioamnionitis via acute or chronic placental membrane inflammation. (8) (12) (14–16) The presence of chorioamnionitis itself may lead to a 2.9–7.6-fold increased risk of HIV MTCT, especially *in-utero* transmission.(8) (14) Additional studies in our same NICHD HPTN 040 cohort of mother-infant pairs demonstrated a significant association between maternal syphilis and HIV MTCT, particularly with *in utero* HIV transmission.(45) (48) Similarly, in a sub-population of nearly 1000 infants studied in our cohort, congenital CMV infection was highly prevalent in the group, particularly among HIV *in utero* infected infants.(46) One hypothesis is that the findings of this study in conjunction with our other NICHD HPTN 040 results may suggest that it is placental inflammation triggered by these infections (CT, CT and NG, syphilis, and/or CMV) that may be facilitating HIV transmission, possibly promoted by immune activation enhancing the expression of CCR5 T-cell receptors that increase viral infectivity. (47)

One limitation of our study was that while maternal CD4 counts and plasma HIV viral load did not differ significantly by STI status, maternal HIV cervicovaginal viral shedding studies were not performed. Since cervicovaginal samples were not collected during the study, we were also unable to test for other reproductive tract infections such as bacterial vaginosis, *T. vaginalis*, and herpes simplex virus. Maternal and congenital syphilis was analyzed previously in another sub-study,(48) while the present manuscript is focused mainly on CT and NG co-infections. However, given the results of all of our sub-analyses, we plan to report results and overlap of infectious disease processes in 040 in a separate publication. This report includes CT, NG, syphilis, and CMV with respect to HIV perinatal transmission. Furthermore, as a sub-study, the sample size was based on convenience. As a result, the

ability to detect small differences in MTCT between STI groups was affected by insufficient power, particularly for our MTCT rates that were <17%. Our sample size for the MTCT analysis was further affected by the 74 (5.4%) infants with unknown HIV status that were lost to follow-up or died prior to the 3 month study endpoint. The lack of HIV status for those infants may have weakened the relationship between STI group and HIV MTCT in our cohort as 14 (18.9%) infants had mothers with an STI.

CONCLUSION

This study provides important information about the prevalence of CT and NG infection among neglected groups such as HIV-infected pregnant women presenting late for care. With 1 in 5 women infected with CT and/or NG in our sample, certain vulnerable groups such as young women with undiagnosed HIV-infection appear to also be at high risk for other STI co-infection during pregnancy. While further studies powered to detect HIV MTCT differences among STI-infected women are needed, this study provides some evidence to suggest that untreated CT and possibly co-infection with CT and NG may be a risk factor for increased HIV MTCT in populations such as ours. Given the improved ability to decrease HIV *intrapartum* MTCT rates to as low as 2% with infant antiretroviral prophylaxis regimens in HIV-infected, late presenting women (as in our NICHD HPTN 040 cohort), perhaps, renewed efforts should be placed on also addressing potential unnecessary risk factors for *in utero* transmission, which may be as high as 9% for high risk mothers with untreated HIV and an STI. Given that screening and treatment of STIs in many countries around the world is not routine and continues to rely on the “syndromic approach,” our study results may also underscore the need for prenatal laboratory-based STI screening and treatment programs in combination with existing efforts to identify pregnant women at high risk for undiagnosed HIV-infection. While more definitive evidence is needed, such programs may aid in preventing adverse pregnancy and neonatal outcomes, including the potential to further minimize the risk of HIV MTCT.

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Contributors Statement Page

Kristina Adachi drafted the initial sub-study design and data analysis, drafted the initial manuscript, revised, and approved the final manuscript as submitted.

Jeffrey Klausner provided oversight for the current sub-study design, data analysis, reviewed, revised, and approved final manuscript as submitted.

Claire Bristow performed the initial data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jiahong Xu designed the data collection instruments, organized data entry for the initial study, and provided all data collected for this study. Jiahong Xu also assisted in providing methods for data analysis, confirmed and finalized primary data analysis study results presented in this paper.

Bonnie Ank assisted with preparation and coordination of urine samples from study sites to Cepheid, Inc. and provided laboratory support in the U.S.

Fred Weir provided direct oversight of specimen analysis at Cepheid. David Persing facilitated specimen analysis at Cepheid.

Mariza Morgado provided laboratory support in Brazil for study conduct, specimen storage, transfer of specimens to the US, and participated in data analysis.

Esau Joao and Jose Henrique Pilotto were responsible for initial study design, patient recruitment and patient care enrolled in this study at sites in Brazil and in South Africa. They also reviewed and revised the manuscript, and approved the final manuscript as submitted.

D. Heather Watts, Valdilea Veloso, Lynne Mofenson, and Karin Nielsen-Saines supervised the design of the data collection instruments, supervised data collection at all sites, critically reviewed the manuscript, and approved of the final manuscript as submitted. Dr. Nielsen-Saines was the principal investigator of the parent study as well as this current sub-study.

Acknowledgment of additional co-authors

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Abbreviations

HIV	human immunodeficiency virus
NICHD	National Institute of Child Health and Human Development
CDC	Center for Disease Control and Prevention
HPTN	HIV Prevention Trials Network
STI	sexually transmitted infection
CT	*Chlamydia trachomatis*
NG	*Neisseria gonorrhoeae*
WHO	World Health Organization
MTCT	mother-to-child transmission

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Table 1

Maternal Demographic, Pregnancy, and HIV-Related Characteristics by STI Status

	Total (N = 1373) n (%)	CT & NG Co-infection (N = 35) n (%)	CT Only (N = 214) n (%)	NG Only (N = 28) n (%)	No STI (N = 1096) n (%)	p-value†
Demographics						
Site						
US	7 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.6)	0.07
Brazil	938 (68.3)	18 (51.4)	142 (66.4)	14 (50.0)	764 (69.7)	
Argentina	19 (1.4)	0 (0.0)	2 (0.9)	0 (0.0)	17 (1.6)	
South Africa	409 (29.8)	17 (48.6)	70 (32.7)	14 (50.0)	308 (28.1)	
Age (years), continuous						
Mean (std. dev.)	26.9(6.4)	27.29 (6.4)	22.9(4.3)	25.4 (6.0)	26.86 (6.0)	<.0001
Median (IQR)	26.0 (22.0–31.0)	26.0 (22.0–32.0)	22.0 (19.0–26.0)	25.0 (21.0–29.0)	26.5 (22.0–30.0)	
Age (years), categorical						
>=30	443 (32.3)	4 (11.4)	48 (22.4)	8 (28.6)	383 (35.0)	0.0001
25–29	376 (27.4)	6 (17.1)	62 (29.0)	8 (28.6)	300 (27.4)	
13–24	554 (40.4)	25 (71.4)	104 (48.6)	12 (42.9)	413 (37.7)	
Occupation						
Employed	240 (17.5)	3 (8.6)	33 (15.5)	6 (21.4)	198 (18.1)	0.67
Unemployed/Homemaker	1056 (77.0)	31 (88.6)	167 (78.4)	21 (75.00)	837 (76.4)	
Other	76 (5.5)	1 (2.9)	13 (6.1)	1 (3.6)	61 (5.6)	
Race/Ethnicity						
White/Other	330 (24.0)	4 (11.4)	46 (21.5)	5 (17.9)	275 (25.1)	0.37
Black	686 (50.0)	23 (65.7)	113 (52.8)	15 (53.6)	535 (48.8)	
Mixed/Mulatto	357 (26.0)	8 (22.9)	55 (25.7)	8 (28.6)	286 (26.1)	
Marital Status						
Single/Unmarried	754 (55.0)	23 (65.7)	124 (58.2)	23 (82.1)	584 (53.3)	0.01
Married/Cohabitation	618 (45.0)	12 (34.3)	89 (41.8)	5 (17.9)	512 (46.7)	
Substance Usage						
Illegal Substance Use						
No	1256 (91.9)	29 (82.9)	195 (91.6)	23 (82.1)	1009 (92.5)	<0.05
Yes	111 (8.1)	6 (17.1)	18 (8.5)	5 (17.9)	82 (7.5)	

	Total (N = 1373) n (%)	CT & NG Co-infection (N = 35) n (%)	CT Only (N = 214) n (%)	NG Only (N = 28) n (%)	No STI (N = 1096) n (%)	p-value†
Alcohol Use						
No	886 (65.1)	20 (57.1)	135 (64.0)	17 (60.7)	714 (65.6)	0.69
Yes	476 (35.0)	15 (42.9)	76 (36.0)	11 (39.3)	374 (34.4)	
Tobacco Use						
No	926 (67.9)	19 (54.3)	133 (63.0)	15 (53.6)	759 (69.6)	0.02
Yes	438 (32.1)	16 (45.7)	78 (37.0)	13 (46.4)	331 (30.4)	
Pregnancy Related Characteristics						
Any Prior Preterm Birth						
No	1114 (81.6)	22 (62.9)	173 (81.2)	18 (64.3)	901 (82.7)	0.002
Yes	252 (18.5)	13 (37.1)	40 (18.8)	10 (35.7)	189 (17.3)	
Any Prior Stillbirth						
No	1312 (95.7)	34 (97.1)	210 (98.6)	27 (96.4)	1041 (95.1)	0.13
Yes	59 (4.3)	1 (2.86)	3 (1.4)	1 (3.6)	54 (4.9)	
Any Prenatal Care						
No	524 (38.3)	24 (68.6)	93 (43.7)	12 (42.9)	395 (36.1)	0.0003
Yes	845 (61.7)	11 (31.4)	120 (56.3)	16 (57.1)	698 (63.9)	
Infant Delivery Status						
Vaginal	903 (65.8)	28 (80.0)	165 (77.1)	25 (89.3)	685 (62.6)	<.0001
Cesarean	469 (34.2)	7 (20.0)	49 (22.9)	3 (10.7)	410 (37.4)	
HIV Related Characteristics						
CD4 Count (cells/mm3)						
Mean (std. dev.)	511.9 (311.1)	505.7 (307.5)	463.3 (278.2)	556.1 (340.7)	479.5 (227.2)	0.14
Median (IQR)	458.0 (291.0–663.0)	445.5 (284.0–649.0)	459.0 (280.0–603.0)	499.0 (325.0–704.0)	428.5 (317.0–705.5)	
HIV Log10 Viral Load (copies/mL)						
Mean (std. dev.)	4.13 (0.8)	4.11 (0.9)	4.27 (0.9)	4.18 (0.8)	4.05 (0.8)	0.44
Median (IQR)	4.2 (3.6–4.7)	4.2 (3.6–4.7)	4.5 (3.7–4.8)	4.2 (3.6–4.8)	4.3 (3.5–4.6)	
Viral Load>20,000 copies/mL	603 (44.1)	20 (57.1)	91 (43.1)	13 (46.4)	479 (43.7)	0.46

†*P*-value is either to test the overall difference in STI prevalence for each categorical variable (Chi-square test) or the median difference of the continuous variables among STI groups. No STI refers to being uninfected with CT, NG, or both CT and NG. Significant differences ($p<0.05$) were noted for STI prevalence when evaluated by maternal age, marital status, illegal substance use, tobacco use, prior preterm birth, prenatal care, and mode of delivery.

Table 2

Logistic Regression Analysis Exploring Relationship of Overall STI (CT and/or NG Co-Infection) with Maternal Demographics, Pregnancy, and HIV-Related Characteristics

	Total (N=1373) n (col %)	Any STI Positive (N=277) n (row %)	Negative (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Study Site							
US	7 (0.5)	0 (0.0)	7 (100)	<0.01 (<0.01 –>999)	0.98		
Brazil	938 (68.3)	174 (18.6)	764 (81.4)	1.00			
Argentina	19 (1.4)	2 (10.5)	17 (89.5)	0.52 (0.12 –2.26)	0.38		
South Africa	409 (29.8)	101 (24.7)	308 (75.3)	1.44 (1.09 –1.90)	0.01		
Maternal Age (years)							
Continuous				0.95 (0.93 –0.97)	<.0001		
30 and Older	443 (32.3)	60 (13.5)	383 (86.5)	1.00		1.00	
25–29	376 (27.4)	76 (20.2)	300 (79.8)	1.62 (1.12 –2.34)	0.01	1.65 (1.13–2.40)	0.010
13–24	554 (40.3)	141 (25.5)	413 (74.5)	2.18 (1.56 –3.04)	<.0001	2.18 (1.55–3.07)	<.0001
Maternal Occupation							
Employed	240 (17.5)	42 (17.5)	198 (82.5)	1.00			
Unemployed/Homemaker	1056 (77.0)	219 (20.7)	837 (79.3)	1.23 (0.86 –1.78)	0.26		
Other	76 (5.5)	15 (19.7)	61 (80.3)	1.16 (0.60 –2.23)	0.66		
Race/Ethnicity							
White/Other	330 (24.0)	55 (16.7)	275 (83.3)	1.00			
Black	86 (50.0)	151 (22.0)	535 (78.0)	1.41 (1.00 –1.98)	0.05		
Mixed/Mulatto	357 (26.0)	71 (19.9)	286 (80.1)	1.24 (0.84 –1.83)	0.28		
Marital Status							
No	754 (55.0)	170 (22.5)	584 (77.5)	1.00			
Yes	618 (45.0)	106 (17.2)	512 (82.8)	0.71 (0.54 –0.93)	0.01		
Illegal Substance Use							
No	1256 (91.9)	247 (19.7)	1009 (80.3)	1.00			
Yes	111 (8.1)	29 (26.1)	82 (73.9)	1.45 (0.93 –2.26)	0.11		
Alcohol Use							
No	886 (65.1)	172 (19.4)	714 (80.6)	1.00			

	Total (N=1373) n (col %)	Any STI Positive (N=277) n (row %)	Negative (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Yes	476 (34.9)	102 (21.4)	374 (78.6)	1.13 (0.86 –1.49)	0.38		
Tobacco Use							
No	926 (67.9)	167 (18.0)	759 (82.0)	1.00		1.00	
Yes	438 (32.1)	107 (24.4)	331 (75.6)	1.47 (1.12 –1.93)	0.01	1.42 (1.07–1.89)	0.01
Prior Preterm Birth							
No	1114 (81.6)	213 (19.1)	901 (80.9)	1.00			
Yes	252 (18.4)	63 (25.0)	189 (75.0)	1.41 (1.02 –1.95)	0.04		
Prior Stillbirth							
No	1312 (95.7)	271 (20.7)	1041 (79.3)	1.00			
Yes	59 (4.3)	5 (8.5)	54 (91.5)	0.36 (0.14 –0.90)	0.03		
Prenatal Care							
No	524 (38.3)	129 (24.6)	395 (75.4)	1.00		1.00	
Yes	845 (61.7)	147 (17.4)	698 (82.6)	0.64 (0.49 –0.84)	0.001	0.74 (0.56–0.98)	0.03
Infant Delivery							
Vaginal	903 (65.8)	218 (24.1)	685 (75.9)	1.00		1.00	
Cesarean	469 (34.2)	59 (12.6)	410 (87.4)	0.45 (0.33 –0.62)	<.0001	0.46 (0.33–0.63)	<.0001
Maternal CD4 Counts (copies/mm3)/100				1.03 (0.99 –1.07)	0.15		
Log10 of Matern al Viral Load				1.10 (0.93 –1.29)	0.26		

No women were excluded in this analysis. The unadjusted logistic regression showed that the study site, maternal age, race/ethnicity, marital status, tobacco use, preterm birth, stillbirth, prenatal care, and mode of infant delivery were associated with overall STI infection. In the adjusted logistic analyses only younger age, tobacco use, lack of prenatal care, and vaginal infant delivery were associated with greater odds of overall STI infection

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Table 3

Logistic Regression Analysis Exploring Relationship of Individual Maternal STIs (CT, NG, and CT & NG Co-Infection) with Maternal Demographics and Pregnancy Parameters

A) Any CT (CT Only + CT & NG Co-Infection): * Excludes NG Only (n=28)

	Total (N=1345) n (col %)	Any CT (N=249) n (row %)	Uninfected (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Maternal Age (years)							
Continuous				0.94 (0.92 –0.96)	<.0001		
30 and Older	435 (32.3)	52 (12.0)	383 (88.0)	1.00		1.00	
25–29	368 (27.4)	68 (18.5)	300 (81.5)	1.67 (1.13 –2.47)	0.01	1.71 (1.15–2.54)	0.01
13–24	542 (40.3)	129 (23.8)	413 (76.2)	2.30 (1.62 –3.27)	<.0001	2.30 (1.61–3.29)	<.0001
Tobacco Use							
No	911 (68.2)	152 (16.7)	759 (83.3)	1.00		1.00	
Yes	425 (31.8)	94 (22.1)	331 (77.9)	1.42 (1.06 –1.89)	0.02	1.36 (1.01–1.82)	0.04
Prior Stillbirth							
No	1285 (95.7)	244 (19.0)	1041 (81.0)	1.00			
Yes	58 (4.3)	4 (6.9)	54 (93.1)	0.32 (0.11 –0.88)	0.03		
Prenatal Care							
No	512 (38.2)	117 (22.9)	395 (77.1)	1.00		1.00	
Yes	829 (61.8)	131 (15.8)	698 (84.2)	0.63 (0.48 –0.84)	0.001	0.71 (0.53–0.96)	0.02
Infant Delivery							
Vaginal	878 (65.3)	193 (22.0)	685 (78.0)	1.00		1.00	
Cesarean	466 (34.7)	56 (12.0)	410 (88.0)	0.48 (0.35 –0.67)	<.0001	0.50 (0.36–0.70)	<.0001

B) Any NG (NG Only + CT & NG Co-Infection): *Excludes CT Only (n= 214)

	Total (N=1159) n (col %)	Any NG (N=63) n (row %)	Uninfected (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Maternal Age (years)							
Continuous				0.93 (0.89 –0.97)	0.002		
30 and Older	395 (34.1)	12 (3.0)	383 (97.0)	1.00		1.00	
25–29	314 (27.1)	14 (4.5)	300 (95.5)	1.49 (0.68 –3.27)	0.32	1.63 (0.74–3.61)	0.23
13–24	450 (38.8)	37 (8.2)	413 (91.8)	2.86 (1.47 –5.56)	0.002	2.97 (1.51–5.84)	0.002

*B) Any NG (NG Only + CT & NG Co-Infection): *Excludes CT Only (n= 214)*

	Total (N=1159) n (col %)	Any NG (N=63) n (row %)	Uninfected (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Illegal Substance Use							
No	1061 (91.9)	52 (4.9)	1009 (95.1)	1.00			
Yes	93 (8.1)	11 (11.8)	82 (88.2)	2.60 (1.31 –5.18)	0.01		
Tobacco Use							
No	793 (68.8)	34 (4.3)	759 (95.7)	1.00		1.00	
Yes	360 (31.2)	29 (8.1)	331 (91.9)	1.96 (1.17 –3.26)	0.01	1.83 (1.08–3.09)	0.02
Prior Preterm Birth							
No	941 (81.6)	40 (4.3)	901 (95.7)	1.00			
Yes	212 (18.4)	23 (10.8)	189 (89.2)	2.74 (1.60 –4.69)	0.0002		
Prenatal Care							
No	431 (37.3)	36 (8.4)	395 (91.6)	1.00		1.00	
Yes	725 (62.7)	27 (3.7)	698 (96.3)	0.42 (0.25 –0.71)	0.001	0.50 (0.30–0.86)	0.01
Infant Delivery							
Vaginal	738 (63.7)	53 (7.2)	685 (92.8)	1.00		1.00	
Cesarean	420 (36.3)	10 (2.4)	410 (97.6)	0.32 (0.16 –0.63)	0.001	0.33 (0.17–0.68)	0.002

*C) CT & NG Co-Infection: *Excludes CT Only (n=214) and NG Only (n=28)*

	Total (N=1131) n (col %)	CT& NG Co-infection (N=35) n (row %)	Uninfected (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Maternal Age (years)							
Continuous				0.87 (0.82 –0.94)	0.0001		
30 and Older	387 (34.2)	4 (1.0)	383 (99.0)	1.00		1.00	
25–29	306 (27.1)	6 (2.0)	300 (98.0)	1.91 (0.54 –6.85)	0.32	2.26 (0.63–8.14)	0.21
13–24	438 (38.7)	25 (5.7)	413 (94.3)	5.80 (2.00–16.81)	0.001	6.24 (2.14–18.3)	0.001
Illegal Substance Use							
No	1038 (91.8)	29 (2.8)	1009 (97.2)	1.00			
Yes	88 (7.8)	6 (6.8)	82 (93.2)	2.55 (1.03 –6.31)	0.04		
Tobacco Use							
No	778 (68.8)	19 (2.4)	759 (97.6)	1.00			
Yes	347 (30.7)	16 (4.6)	331 (95.4)	1.93 (0.98 –3.80)	0.06		

*C) CT & NG Co-Infection: *Excludes CT Only (n=214) and NG Only (n=28)*

	Total (N=1131) n (col %)	CT& NG Co-infection (N=35) n (row %)	Uninfected (N=1096) n (row %)	Unadjusted		Adjusted	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Prior Preterm Birth							
No	923 (81.6)	22 (2.4)	901 (97.6)	1.00			
Yes	202 (17.9)	13 (6.4)	189 (93.6)	2.82 (1.39 –5.69)	0.004		
Prenatal Care							
No	419 (37.0)	24 (5.7)	395 (94.3)	1.00		1.00	
Yes	709 (62.7)	11 (1.6)	698 (98.4)	0.26 (0.13 –0.54)	0.0003	0.31 (0.15–0.67)	0.003
Infant Delivery							
Vaginal	713 (63.0)	28 (3.9)	685 (96.1)	1.00			
Cesarean	417 (36.9)	7 (1.7)	410 (98.3)	0.42 (0.18 –0.96)	0.04		

Logistic regression was done to evaluate the relationship of each STI group (any CT, any NG, and CT & NG co-infected) with maternal demographic, pregnancy, and HIV-related parameters (study site, maternal age, occupation, race/ethnicity, marital status, illegal substance use, alcohol use, tobacco use, prior preterm birth, prior stillbirth, prenatal care, mode of delivery, CD4 count, and log10 of HIV viral load). Only parameters found to be significant are displayed above.

A) Part A of the table analyzes the relationship between any CT-infection (CT only, CT & NG co-infected) versus those uninfected with any STI with respect to maternal demographic, pregnancy, and HIV-related characteristics. Mothers with NG only were excluded from this analysis. Only significant findings are displayed. The unadjusted logistic regression demonstrated that study site, maternal age, tobacco use, prior stillbirth, prenatal care status, and mode of infant delivery were associated with CT infection. However, the adjusted logistic regression analyses demonstrated that only younger age, tobacco use, no prenatal care, and vaginal delivery were associated with greater odds of CT infection.

B) Part B of the table analyzes relationship between any NG-infection (NG only, CT & NG co-infected) versus those uninfected with any STI with respect to maternal demographic, pregnancy, and HIV-related characteristics. Mothers with CT only were excluded from analysis. Only significant findings are displayed. The unadjusted logistic regression showed that study site, maternal age, race/ethnicity, marital status, illegal substance use, tobacco use, prior preterm birth, prenatal care status, and mode of delivery were associated with NG infection. However, the adjusted logistic analyses showed that younger age, tobacco use, no prenatal care, and vaginal infant delivery were associated with greater odds of NG infection.

C) Part C of the table analyzes relationship between mothers with CT & NG co-infection versus those uninfected with any STI with respect to maternal demographic, pregnancy, and HIV-related characteristics. CT only as well as NG only mothers were excluded from analysis. Only significant findings are displayed. The unadjusted logistic regression showed that the study site, maternal age, race/ethnicity, illegal substance use, tobacco use (marginal significance), prior preterm birth, prenatal care status, and infant delivery type were associated with CT & NG co-infection. The adjusted logistic analyses showed that only younger age and no prenatal care were associated with the greater odds of CT & NG co-infection.

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Table 4

Distribution of Maternal STI Status and HIV MTCT

	Total n (%)	Any STI (CT, NG, or CT & NG Co-Infected)	CT & NG Co-Infected n (%)	CT Only n (%)	NG Only n (%)	No CT & NG Infection n (%)	p-value
Maternal STI Infection	1373 (100.0)	277 (20.2)	35 (2.6)	214 (15.6)	28 (2.0)	1096 (79.8)	-----
Total Infant HIV Infection	117 (8.5)	28 (10.1)	5 (14.3)	23 (10.7)	0 (0)	89 (8.1)	0.04
HIV-Infected *In Utero*	75 (5.5)	19 (6.9)	3 (8.6)	16 (7.5)	0 (0.0)	56 (5.1)	0.02
HIV-Infected *Intrapartum*	42 (3.1)	9 (3.2)	2 (5.7)	7 (3.3)	0 (0.0)	33 (3.0)	< 0.05
HIV Uninfected	1182 (86.1)	235 (84.5)	24 (68.6)	183 (85.5)	28 (100.0)	947 (86.4)	----
HIV Status Unknown	74 (5.4)	14 (5.1)	6 (17.1)	8 (3.7)	0 (0.0)	60 (5.5)	-----

This table evaluates the distribution of HIV MTCT by maternal STI group. In the frequency distribution above, p-values were from the exact test with Monte Carlo simulations. A p-value of 0.05 or less indicates that at least one significant finding among four STI infection groups was detected among all infants. Significant differences were noted among STI groups for rates of overall HIV MTCT as well as for *in utero* and *intrapartum* HIV MTCT.

Table 5

Logistic Regression Analysis of Maternal STI Status and HIV MTCT

	Total n (col. %)	HIV Infected Infant n (row %)	HIV Uninfected Infant n (row %)	OR (95% CI)	p-value
HIV Status Among Total Cohort	1373 (100.0)	117 (8.5)	1256 (91.5)	---	---
A) Analysis for Total Cohort (n=1373)					
No STI (No CT, NG Infection)	1096 (79.8)	89 (8.1)	1007 (91.9)	1.00	----
CT & NG Co-Infection	35 (2.6)	5 (14.3)	30 (85.7)	1.89 (0.56–5.08)	0.32
CT Only	214 (15.6)	23 (10.8)	191 (89.3)	1.36 (0.80–2.24)	0.26
NG Only	28 (2.0)	0 (0.0)	28 (100.0)	0.29 (0.00–1.30)	0.19
Any CT Infection					
No	1124 (81.9)	89 (7.9)	1035 (92.1)	1.00	----
Yes	249 (18.1)	28 (11.2)	221 (88.8)	1.47	0.09
Any NG Infection					
No	1310 (95.4)	112 (8.6)	1198 (91.5)	1.00	---
Yes	63 (4.6)	5 (7.9)	58 (92.1)	0.92 (0.36–2.35)	0.86
B) Subset Analysis: HIV In Utero Infected Infants (n=1331) **Excludes Intrapartum Infected Infants*					
No STI (No CT, NG Infection)	1063 (79.9)	56 (5.3)	1007 (94.7)	1.00	---
CT & NG Co-Infected	33 (2.5)	3 (9.1)	30 (90.9)	1.80 (0.34–6.06)	0.52
CT Only	207 (15.6)	16 (7.7)	191 (92.3)	1.51 (0.79–2.73)	0.22
NG Only	28 (2.1)	0 (0.0)	28 (100.0)	0.45 (0.00–2.09)	0.45
Any CT Infection					
No	1091 (82.0)	56 (5.1)	1035 (94.9)	1.00	---
Yes	240 (18)	19 (7.9)	221 (92.1)	1.59 (0.93–2.73)	0.09
Any NG Infection					
No	1270 (95.4)	72 (5.7)	1198 (94.3)	1.00	---
Yes	61 (4.6)	3 (4.9)	58 (95.1)	0.86 (0.26–2.81)	0.80
C) Subset Analysis: HIV Intrapartum Infected Infants (n=1298) **Excludes In Utero Infected Infants*					
No STI (No CT, NG Infection)	1040 (80.1)	33 (3.2)	1007 (96.8)	1.00	---
CT & NG Co-Infected	32 (2.5)	2 (6.3)	30 (93.8)	2.03 (0.23–8.61)	0.56

	Total n (col. %)	HIV Infected Infant n (row %)	HIV Uninfected Infant n (row %)	OR (95% CI)	p-value
CT Only	198 (15.3)	7 (3.5)	191 (96.5)	1.12 (0.41–2.62)	0.93
NG Only	28 (2.2)	0 (0.0)	28 (100.0)	0.77 (0.00–3.60)	0.82
Any CT Infection					
No	1068 (82.3)	33 (3.1)	1035 (96.9)	1.00	---
Yes	230 (17.7)	9 (3.9)	221 (96.1)	1.28 (0.60–2.71)	0.52
Any NG Infection					
No	1238 (95.4)	40 (3.2)	1198 (96.8)	1.00	---
Yes	60 (4.6)	2 (3.3)	58 (96.7)	1.0 (0.24–4.38)	0.96

This table evaluates the relationship between maternal STI groups and HIV MTCT. In sub-analysis (B & C) the relationship between maternal STI group was also evaluated with respect to HIV *in utero* and HIV *intrapartum* MTCT. The OR, 95% CI, and p-values were from exact logistic models. The probability modeled is HIV=1. An OR=1.47 (P=0.09) indicates that the infants born to mothers who were CT infected are about 1.5 times more likely to be co-infected with HIV (marginally significant). Similar findings were detected (OR=1.59, P=0.09) in the subset analysis for *in utero* infected infants (marginally significant).