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Intrapartum Antibiotic Exposure and Early Neonatal Morbidity and Mortality in Africa

George Kafulafula, MBBS, FCOG(SA), MMed[1], **Anthony Mwatha, MS**[2], **Ying Qing Chen, PhD**[2], **Said Aboud, MD**[3], **Francis Martinson, MD, PhD**[4], **Irving Hoffman, PA, MPH**[4], **Wafaie Fawzi, MD, DrPH**[5], **Jennifer S. Read, MD, MS, MPH**[6], **Megan Valentine, PA-C, MS**[7], **Kasonde Mwinga, MBChB, MMed, MPH**[8], **Robert Goldenberg, MD**[9], and **Taha E. Taha, MD, PhD**[10]

[1] Department of Obstetrics and Gynecology, College of Medicine, University of Malawi, Blantyre, Malawi

[2] SCHARP, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[3] Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[4] Center for Infectious Diseases, University of North Carolina, Chapel Hill, NC, USA

[5] Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

[6] Pediatric, Adolescent, and Maternal AIDS Branch, Eunice Kennedy Shriver NICHD, NIH, DHHS; Bethesda, MD, USA

[7] Family Health International, Research Triangle Park, NC, USA

[8] University Teaching Hospital, Department of Pediatrics and Child Health, Lusaka, Zambia

[9] Department of Obstetrics and Gynecology, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA

[10] Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

Abstract

Background—Infants born to women who receive intrapartum antibiotics may have higher rates of infectious morbidity and mortality than unexposed infants.

Objective—To determine the association of maternal intrapartum antibiotics and early neonatal morbidity and mortality.

Methods—Secondary analysis of data from a multi-site randomized placebo-controlled clinical trial of antibiotics to prevent chorioamnionitis-associated mother-to-child transmission of HIV-1 and preterm birth in sub-Saharan Africa. Early neonatal morbidity and mortality were analyzed. In an intent-to-treat (ITT) analysis, infants born to women randomized to antibiotics or placebo were compared. Additionally, non-ITT analysis was performed because some women received non-study antibiotics for various clinical indications.

Correspondence: Dr George Kafulafula, Department of Obstetrics & Gynecology, College of Medicine, University Of Malawi, Private Bag 360, Chichiri, Blantyre 3, Malawi, Telephone: (265) 1 878 090, Fax: (265) 1 870 132, gkafulafula@jhu.medcol.mw.

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Results—Overall, 2659 pregnant women were randomized. Of these, 2466 HIV-1-infected and -uninfected women delivered 2413 live born and 84 stillborn infants. In the ITT analysis, there were no significant associations between exposure to antibiotics and early neonatal outcomes. Non-ITT analyses showed more illness at birth (11.2% vs. 8.6%, p=0.03) and more admissions to the Special Care Baby Unit (12.6% vs. 9.8%, p = 0.04) among infants exposed to maternal intrapartum antibiotics than among unexposed infants. Further analyses revealed greater early neonatal morbidity and mortality among infants of mothers who received non-study antibiotics than of mothers who received study antibiotics.

Conclusion—There is no association between intrapartum exposure to antibiotics and early neonatal morbidity or mortality. The associations observed in non-ITT analyses are most likely the result of women with peripartum illnesses being more likely to receive non-study antibiotics.

Keyword/Category

Antibiotic resistance; Antibiotics; Neonatal morbidity; Neonatal mortality; Neonatal sepsis

INTRODUCTION

Perinatal mortality and morbidity are significant global health problems. The major causes of perinatal deaths include preterm birth, neonatal infection and asphyxia[1, 2]. However, the roles of other factors that may predispose neonates to these direct causes of mortality are less well understood. Pregnant women may receive antibiotics during the antepartum period or during labor for various reasons, including treatment of syphilis and bacterial vaginosis (BV) or the prevention of preterm labor and adverse outcomes associated with pre-labor rupture of membranes (PROM). Such treatment with antibiotics may benefit the neonate either by eliminating maternal infection or by treating intrauterine fetal infection if the antibiotic crosses the placenta. In such cases, there is a clear benefit to the baby. However, it is also known that intrapartum antibiotic use may be associated with adverse effects in late neonatal life, including increased frequency of neonatal infection and necrotizing enterocolitis[3] or delayed clinical or microbiological diagnosis of neonatal infections and development of antibiotic resistance[4–6]. These reports do not differentiate early from late onset neonatal morbidity and mortality that may result from intrapartum antibiotic exposure. There is also a possibility that transplacental transfer of antibiotics used for maternal indications may result in sub-therapeutic levels in the neonate and contribute to early neonatal morbidity. This may in turn increase the number of neonates admitted to and who die in a special care baby unit, due to early neonatal disease.

We therefore analyzed data from a randomized clinical trial of antibiotics to reduce chorioamnionitis-related mother-to-child transmission (MTCT) of HIV and preterm birth[7]. In this trial, mothers received antibiotics (erythromycin and metronidazole) antepartum starting at 20–24 weeks gestation and intrapartum (ampicillin and metronidazole) starting at onset of labor. The antibiotics were chosen to ensure broad coverage against microorganisms associated with BV, trichomoniasis and chorioamnionitis. The rates of BV and trichomoniasis[8] were reduced in the antibiotic group compared to the placebo group. However, the rates of chorioamnionitis were not different following treatment with these antibiotics[8]. This may be because the antibiotics were administered late after the subclinical (histological) chorioamnionitis was already established. In a planned secondary analysis, we hypothesized that infants born to women who received intrapartum antibiotics would have higher rates of infectious morbidity and mortality than would infants born to women who did not receive intrapartum antibiotics. The main objective of this analysis was to evaluate the association between intrapartum exposure to antibiotics and early neonatal health.

METHODS

Study design, population and procedures

HPTN 024 was a randomized, double blind, placebo-controlled, phase III study of antibiotics to reduce MTCT of HIV. This trial has been previously described in detail[7–8]. It was conducted in four African sites: Blantyre and Lilongwe (Malawi), Lusaka (Zambia) and Dar es Salaam (Tanzania). Enrollment began in July 2001, and the last delivery occurred in August 2003. This study was approved by appropriate Institutional Review Boards in Zambia, Malawi, and Tanzania and in the U.S. at Johns Hopkins University, University of Alabama at Birmingham, University of North Carolina at Chapel Hill, and Harvard University. All women were counseled and provided written informed consent.

Enrollment of HIV-1-infected women at 20–24 weeks' gestation was based on serologically confirmed HIV-1 infection status. In addition to HIV-1-infected women, HIV-1-uninfected women were enrolled at three of the four study sites (one HIV-1-uninfected woman for every five HIV-1-infected women enrolled). HIV-1-uninfected women were included in the trial to reduce stigma among HIV-1-infected women enrolled in the study, and to ensure generalizability of results of the study, especially with regard to the effect of antibiotic treatment on preterm birth[8].

At 20–24 weeks of pregnancy, all enrolled women received either antibiotics (metronidazole 250 mg and erythromycin 250 mg) or identically appearing placebos, all drugs administered orally three times a day for seven days. With the onset of labor contractions and/or pre-labor rupture of membranes (PROM), study participants initiated a second oral course of antibiotics consisting of metronidazole 250 mg and ampicillin 500 mg, or identically appearing placebos, every four hours until delivery and continued postpartum for a total of seven days. When data presented at an interim Data Safety and Monitoring Board review justified the conclusion that the antibiotic regimen did not reduce MTCT of HIV-1, the protocol team was advised to cease enrollment; thus no further participants were recruited as of February 21, 2003. No further antibiotics were administered after this decision was made and therefore some enrolled women did not receive study intrapartum antibiotics.

HIV-1-infected women were provided with nevirapine (NVP) prophylaxis according to the HIVNET 012 regimen[9]. Women also received antibiotic treatment for any clinical indication for which an antibiotic was indicated. Structured questionnaires were used to collect information on maternal demographics, obstetric history, medical history, sexual history, as well as use of concomitant antibiotics and other medications.

Study population and definitions for this analysis

The inclusion criterion for this analysis was: live born infants born to women (both HIV-1-infected and uninfected) enrolled in the HPTN 024 trial. The initial analysis was based on intention-to-treat (ITT). However, some women who were randomized to the treatment arm did not receive study antibiotics (mainly because they did not deliver at the study clinic) while other women randomized to placebo arm received (non-study) antibiotics. Therefore, further analysis based on "*actual" maternal receipt or non-receipt* of intrapartum antibiotics also was performed (non-ITT analysis). To determine the actual receipt of antibiotics by women enrolled in HPTN 024, we reviewed both generic and brand names of antimicrobial agents recorded on the study concomitant medication form. Early neonatal morbidity included outcomes occurring within the first seven days of life, based on the following variables: infant illness at birth, admission to SCBU and duration of stay, and neonatal infections. Early neonatal mortality meant deaths within the first seven days of life. Since admission to SCBU information was extracted from the infant birth form, the analysis of this variable was restricted to infants born

in the study hospital (88.1% antibiotic arm and 86.6% in the placebo arm, p= 0.25). Similarly, discharge status refers to those admitted to the SCBU. The main trial was not designed to detect associations between intrapartum antibiotics and neonatal morbidity and mortality. For this secondary analysis, no separate power calculations were conducted.

Statistical analysis

Statistical analyses were conducted using SAS version 8.2. Independent two sample T-tests, Fischer's exact test and two sample chi-square tests were performed to compare means and medians, respectively. Proportions of neonatal characteristics and outcomes were compared using chi-square tests. Univariate logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the associations of intrapartum antibiotics and neonatal outcomes.

RESULTS

Size and Characteristics of the Study Population

Overall, 2659 pregnant women were randomized antenatally. Of these, 193 were excluded, and the remaining 2466 women delivered 2497 infants. Eighty-four infants (40 in the placebo arm and 44 in the antibiotics arm) were excluded because they were stillborn. This analysis is restricted to 2413 live born infants. Of these 1214 (166 from HIV-1-uninfected and 1048 from HIV-1-infected mothers) were born to 1197 mothers randomized to antibiotics and 1199 (169 from HIV-1-uninfected, 1030 from HIV-1-infected mothers) were born to 1187 mothers in the placebo arm (Figure 1). There were no significant differences in the maternal and infant characteristics according to randomization arm (Table 1).

Analyses of Intrapartum Antibiotics and Early Neonatal Outcomes

In the ITT analysis, there were no differences between maternal intrapartum antibiotic receipt and early neonatal morbidity and mortality (Table 2). The non-ITT cohort was defined as infants born to women who either received or did not receive antepartum and intrapartum antibiotics (including non-study antibiotics). The antibiotics used were penicillins (ampicillin, crystalline penicillin, benzathine penicillin, amoxicillin, cloxacillin), metronidazole, chloramphenicol, cotrimoxazole, erythromycin and gentamicin. The antibiotics were used for cesarean section prophylaxis, PROM and chorioamnionitis, respiratory tract infections (pneumonia, bronchitis, and upper respiratory tract infection), malaria, sepsis (breast abscess, Bartholin's abscess and paronychia), lower genital tract infection (BV and trichomoniasis), genital ulcer disease including syphilis, gastroenteritis including dysentery and urinary tract infection. In the non-ITT analysis (based on the *actual receipt of antibiotics* Table 3), there were more infant illnesses at birth among those born to mothers who received intrapartum antibiotics than among those born to women who did not receive antibiotics (p = 0.03). Most of the infant illnesses occurring at birth were infections, including congenital pneumonia, neonatal sepsis, pyrexia of unknown etiology and umbilical cord infection. The non-infectious illnesses were asphyxia, respiratory distress syndrome, neonatal jaundice, hepatosplenomegaly, hypoglycemia, hypothermia, hypoxic encephalopathy, transient apnea of the newborn, dysmaturity, umbilical cord hemorrhage and, more rarely, congenital anomalies such as anal atresia. In addition, the number of infants admitted to SCBU was significantly higher in neonates exposed to intrapartum antibiotics than neonates who were not exposed to antibiotics (p = 0.04). However, differences in early neonatal infection, duration of stay in SCBU, early neonatal deaths and deaths due to infectious causes were not statistically significant in the two groups.

There were no statistically significant differences between infants exposed and not exposed to intrapartum antibiotics and neonatal infections occurring within the first week of birth, duration

of stay in the special care baby unit, death before discharge or status at discharge from hospital. There were also no statistically significant differences in the reported causes of death for the infants who died in the SCBU (data not shown). The cause of death was in most cases based on clinical judgment by the investigators at the study sites. The commonest cause was infections [15.5% (13/84)] followed by congenital anomalies [7.1% (6/84)]. Although the proportion of deaths due to an infectious etiology among the exposed infants was higher in the exposed group (8/37 or 21.6%) than the unexposed (5/47 or 10.6%), this difference was not statistically significant (p= 0.23), Table 3.

With respect to HIV-1 infection status of the mother and infant HIV-1 exposure at birth, the maternal and infant characteristics and rates of neonatal infections and neonatal deaths were similar in neonates exposed to intrapartum antibiotics compared to the antibiotic unexposed group (data not shown). This was true for both analyses based on ITT and non-ITT. However, the frequency of neonatal infections among neonates with unknown HIV-1 infection status at birth (5.6% vs. 0%, p=0.02) was higher among those whose mothers received intrapartum antibiotics (Table 3).

Additional non-ITT analyses were performed to further evaluate early neonatal outcomes according to not only maternal receipt or non-receipt of intrapartum antibiotics, but also according to whether, if intrapartum antibiotics were received, these were study antibiotics or non-study antibiotics (Table 4). There were three categories of intrapartum antibiotic receipts: “yes” - received *study* antibiotics, “yes” - received *non-study* antibiotics, and “no” - did not receive antibiotics at all. The proportion of mothers who delivered at a study hospital differed significantly according to maternal intrapartum antibiotic receipt category. Similarly, all infant characteristics at birth (except gender) varied significantly according to maternal intrapartum antibiotic receipt: birth weight, Ballard score, Apgar score, and infant illness at birth. Two infant outcomes varied by maternal intrapartum antibiotic receipt category: admission to the SCBU and early neonatal mortality.

Additionally, mothers who received non-study antibiotics were more likely to have rupture of membranes > 4 hours (31.6%) than mothers who received study antibiotics (20.2%) or no antibiotics (17.2%) (p<0.0001). Women who received non-study antibiotics also were more likely to have clinical and histological chorioamnionitis (1.3% and 40.4%, respectively) than women who received study antibiotics (0.3% and 35.9%, respectively) or no antibiotics (0.2% and 34.5%, respectively). The differences in clinical chorioamnionitis among the three groups of women were statistically significant (p=0.04) but not significant (p=0.37) for histological chorioamnionitis. The proportion of infants who died of infectious causes and born to mothers who received or did not receive antibiotics were not significantly different (26.1% [95% CI 8.1 – 44.0], 14.3% [95% CI 0 – 32.6] and 10.6% [95% CI 1.8 – 19.4] if the mother received, respectively, study antibiotic, non-study antibiotic and no antibiotic, p=0.27), Table 4.

DISCUSSION

In the ITT analysis, there were no effects observed between maternal intrapartum receipt of antibiotics and early neonatal morbidity or mortality. In non-ITT analyses, a greater proportion of infants born to women who received intrapartum antibiotics had illnesses at birth and admission to the SCBU. However, upon further analysis i.e. intrapartum antibiotic receipt categorization analysis (Table 4), the greatest early neonatal morbidity and mortality were observed among those infants whose mothers received non-study antibiotics, compared to infants of mothers who received study antibiotics or who did not receive antibiotics at all. These results suggest sicker women, who received antibiotics for a reason other than participation in and randomization to antibiotics, had infants with greater early neonatal morbidity and mortality because of the underlying maternal illness – and not because of exposure to the

antibiotics *per se*. This interpretation is supported by the observation that more mothers with prolonged rupture of membranes (and subsequently chorioamnionitis) were among those who received antibiotics. It is a common practice in obstetrics to treat women with PROM and chorioamnionitis with antibiotics.

Other studies have shown increased risks of neonatal sepsis due to drug-resistant microorganisms among infants of mothers treated with intrapartum antibiotics compared to unexposed infants[6,10,11]. The underlying mechanism may be a sub-therapeutic antibiotic level in such infants. Contrary to these findings, we did not find increased rates of neonatal infection associated with maternal intrapartum antibiotic receipt, perhaps because we confined our analysis to the early neonatal period. Additionally, diagnostic capabilities were limited at the study sites where most of the neonatal outcomes were based on clinical criteria and laboratory confirmation was not consistently available. Bacterial resistance testing was not performed. Therefore, under-estimation of early neonatal morbidity may have occurred.

Infants may become exposed to maternal antibiotics either through the placental route or through breast milk. In the areas where this study was performed, breastfeeding is nearly universal[12] and is usually initiated soon after birth. Previously published data have suggested an increased risk for late onset neonatal sepsis in infants exposed to peripartum antibiotics[4]. Our analysis showed no association between exposure to intrapartum antibiotics and early neonatal infection. This finding is similar to previous reports that did not find evidence of potential adverse effects of intrapartum antibiotics and late onset neonatal disease. However, our data suggest there may not be a difference in the adverse outcomes of antibiotics between late onset and early onset infectious morbidity and mortality. This finding means that clinicians may be more comfortable addressing early neonatal life safety concerns when prescribing antibiotics for pregnant women intrapartum. They should be more able than before to give appropriate advice when asked questions such as, “Will my baby be alright doctor if I take these antibiotics during labor?”.

Further evaluation of the role of intrapartum antibiotics on early neonatal morbidity and mortality as the primary outcome in resource-constrained settings is needed. The design of such studies should take into account confounding factors such as PROM and other maternal infectious conditions that are firstly, indications of antibiotics in the intrapartum period and, secondly, determinants of early neonatal infectious morbidity and mortality. The influence of both maternal and infant HIV infection in these populations should be part of the focus for future studies. Such data may be invaluable in both clarifying the contradictory findings in the literature and in guiding more rational antibiotic use in pregnancy and labor in resource-limited countries.

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HPTN 024 Team: ***Protocol Co-Chairs:*** Taha E. Taha, MD, PhD (Johns Hopkins University Bloomberg School of Public Health); Robert Goldenberg, MD (University of Alabama at Birmingham); ***In-Country Co-Chairs/ Investigators of Record:*** Newton Kumwenda, PhD, George Kafulafula, MBBS, FCOG (Blantyre, Malawi); Francis Martinson, MD, PhD (Lilongwe, Malawi); Gernard Msamanga, MD, ScD (Dar es Salaam, Tanzania); Moses Sinkala, MD, MPH, Jeffrey Stringer, MD (Lusaka, Zambia); *US Co-Chairs:* Irving Hoffman, PA, MPH (University of North Carolina, Chapel Hill); Wafaie Fawzi, MD, DrPH (Harvard School of Public Health); ***In-Country Investigators, Consultants, and Key Site Personnel:*** Robin Broadhead, MBBS, FRCP, George Liomba, MBBS, FRCPath, Johnstone Kumwenda, MBChB, MRCP, Tsedal Mebrahtu, ScM, Pauline Katundu, MHS, Maysoon Dahab, MHS (Blantyre, Malawi); Peter Kazembe, MBChB, David Chilongozi, CO, MPH, Charles Chasela, CO, MPH, George Joaki, MD, Willard Dzinyemba, Sam Kamanga (Lilongwe, Malawi); Elgius Lyamuya, MD, PhD, Charles Kilewo, MD, MMed, Karim Manji, MD, MMed, Sylvia Kaaya, MD, MS, Said Aboud, MD, MMed, Muhsin Sheriff, MD, MPH, Elmar Saathoff, PhD, Priya Satow, MPH, Illuminata Ballonzi, SRN, Gretchen Antelman, ScD, Edgar Basheka, Bpharm (Dar es Salaam, Tanzania); Victor Mudenda, MD, Christine Kaseba, MD, Maureen Njobvu, MD, Makungu Kabaso, MD, Muzala Kapina, MD, Anthony Yeta, MD, Seraphine Kaminsa, MD, MPH, Constantine Malama, MD, Dara Potter, MBA, Maclean Ukwimi, RN, Alison Taylor, BSc, Patrick Chipaila, MSc, Bernice Mwale, Bpharm (Lusaka, Zambia); ***US Investigators, Consultants, and Key Site Personnel:*** Priya Joshi, BS, Ada Cachafeiro, BS, Shermalyn Greene, PhD, Marker Turner, BS, Melissa Kerkau, BS, Paul Alabanza, BS, Amy James, BS, Som Siharath, BS, Tiffany Tribull, MS (UNC-CH); Saidi Kapiga, MD, ScD, George Seage, PhD (HSPH); Sten Vermund, MD, PhD, William Andrews, PhD, MD, Deedee Lyon, BS, MT(ASCP) (UAB); ***NIAID Medical Officer:*** Samuel Adeniyi-Jones, MD; ***NICHD Medical Officer:*** Jennifer S. Read, MD, MS, MPH, DTM&H; ***Protocol Pharmacologist:*** Scharla Estep, RPh, MS; ***Protocol Statisticians:*** Elizabeth R. Brown, ScD, Thomas R. Fleming, PhD, Anthony Mwatha, MS, Lei Wang, PhD, Ying Q. Chen, PhD; ***Protocol Virologist:*** Susan Fiscus, PhD; ***Protocol Operations Coordinator:*** Lynda Emel, PhD; ***Data Coordinators:*** Debra J. Lands, Ed.M, Ceceilia J. Dominique; ***Systems Analyst Programmers:*** Alice H. Fisher, BA, Martha Doyle; ***Protocol Specialist:*** Megan Valentine, PA-C, MS.

Abbreviations

SCBU
special care baby unit

ITT
intent-to-treat analysis

PROM
prelabor rupture of membranes

HPTN
HIV Prevention Trials Network

OR
odds ratio

CI
confidence interval

MTCT
mother-to-child transmission

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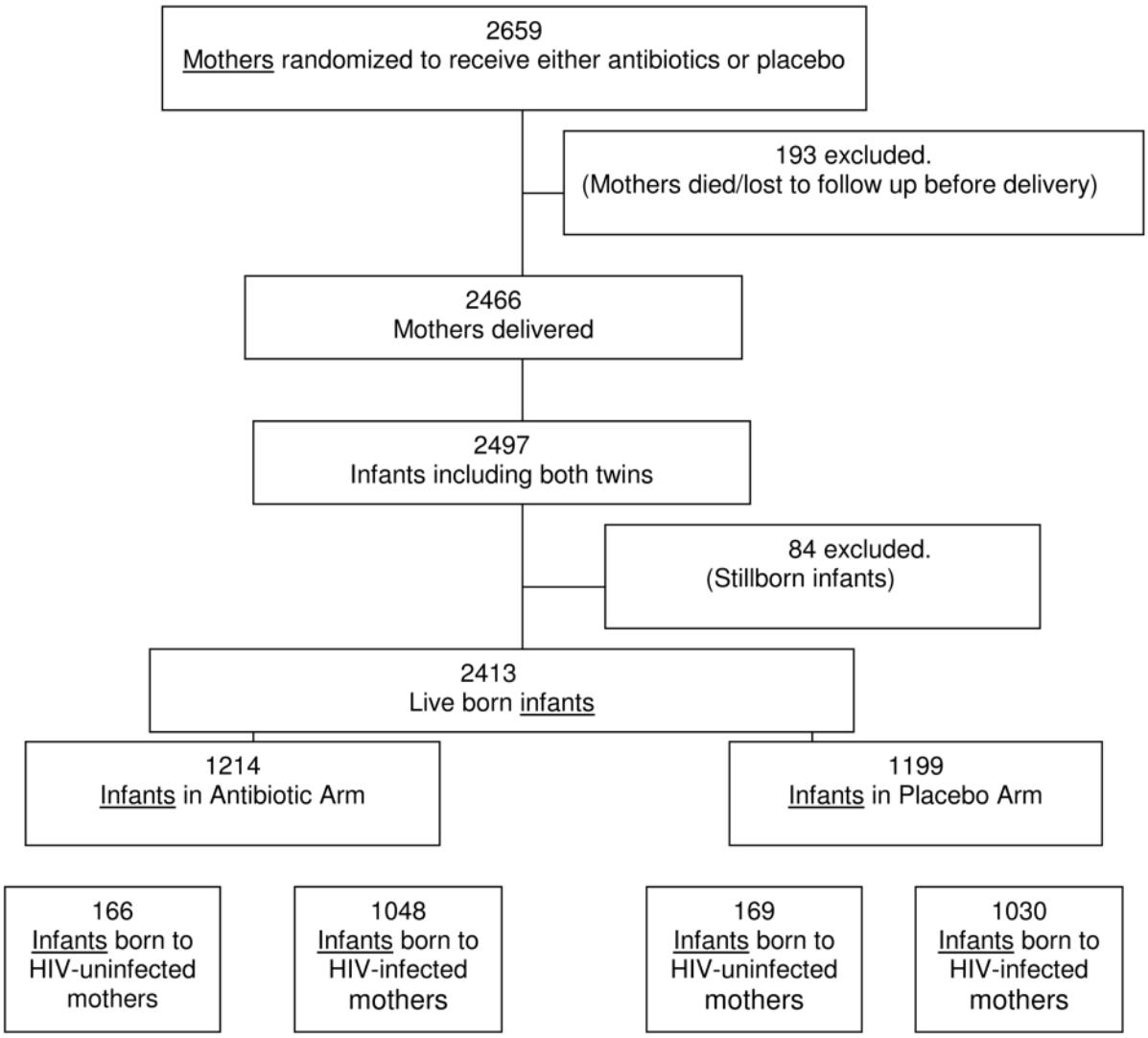

Figure 1.
Randomization profile of mothers and infants in HPTN 024 Study.

Table 1

Characteristics of women randomized to antibiotic or placebo arm and of infants according to maternal randomization arm (ITT analysis).

Characteristic	Category	Antibiotic Arm		Placebo Arm	
MOTHERS		(N=1197)		(N=1187)	
		n/N	%	n/N	%
Age (years)	Mean [SE]	25.0 [0.14]		24.9 [0.14]	
Mode of delivery	Vaginal	1132/1195	94.7	1111/1187	93.6
Mother can read	Yes	953/1197	78.1	919/1187	77.4
HIV infection status	Uninfected	163/1197	13.6	168/1187	14.2
	Infected	1034/1197	86.4	1019/1187	85.8
Hemoglobin	Mean	10.3		10.2	
Prelabor rupture of membranes (PROM)	> 4 hrs	220/1143	19.2	219/1133	19.3
Clinical chorioamnionitis		4/1055	0.4	2/1029	0.2
Histological chorioamnionitis		358/1005	35.6	343/975	35.2
Baseline Bacterial vaginosis		524/1177	44.5	540/1166	46.3
Visit 2 Bacterial vaginosis		275/1156	23.8	420/1132	37.1
INFANTS		(N=1214)		(N=1199)	
Birth weight (g)	Mean [SE]	2937 [16.70]		2955 [17.09]	
Ballard Score	Mean [SE]	38.3 [0.08]		38.4 [0.08]	
Apgar score	1 min	8.3 [0.04]		8.3 [0.04]	
	5 min	9.5 [0.04]		9.6 [0.04]	
Mother HIV infection status	Positive	1034/1197	86.4	1019/1187	85.8

Table 2

Early neonatal morbidity and mortality according to maternal receipt of intrapartum antibiotics (ITT analysis).

Outcome	Category	Antibiotics Arm (N=1214)		Placebo Arm (N=1199)		Odds ratio [95% CI]
		n/N	%	n/N	%	
Infant illness at birth	Yes	122/1212	10.1	111/1194	9.3	1.1 [0.8 – 1.4]
Admission to SCBU[a]	Yes	112/1070	10.5	121/1036	11.7	0.95 [0.7 – 1.2]
Early neonatal infection	Yes	123/1214	10.1	118/1199	9.8	1.0 [0.8 – 1.3]
Duration of SCBU stay (days)[b]	Mean	4.9	-	6.3		0.08[c]
Early neonatal death	Yes	46/1214	3.8	38/1199	3.2	1.2 [0.8 – 1.9]
Vital status at discharge from SCBU[b]	Dead	31/112	27.7	24/119	20.2	
	Alive and unwell	2/112	5.4	8/119	6.7	
	Alive and well	75/112	67.0	87/119	73.1	

[a] SCBU= Special Care Baby Unit

[b] Among those admitted to SCBU

[c] Wilcoxon

Table 3

Early neonatal morbidity and mortality according to maternal intrapartum antibiotic receipt (non-ITT analysis; *actual receipt* of antibiotics analysis).

Outcome	Category	Maternal Receipt of Intrapartum Antibiotics (N=1033)		No Maternal Receipt of Intrapartum Antibiotics (N=1380)		Odds ratio [95% CI]	P-value
		n/N	%	n/N	%		
Infant illness at birth	Yes	115/1031	11.2	118/1375	8.6	1.3 [1.0 – 1.8]	0.03
Admission to SCBU[a]	Yes	117/925	12.6	116/1181	9.8	1.4 [1.1 – 1.9]	0.04
Early neonatal infection	Yes	104/1033	10.1	137/1380	9.9	1.0 [0.8 – 1.3]	0.91
Duration of SCBU stay (days)[b]	Mean	5.3	-	-	6	0.80[c]	0.80[c]
Early neonatal death	Yes	37/1033	3.6	47/1380	3.4	1.1 [0.7 – 1.6]	0.82
	Dead	30/116	25.9	25/115	21.7		
Vital status at discharge from SCBU[b]	Alive and unwell	9/116	7.8	5/115	4.3		0.37
	Alive and well	77/116	66.4	85/115	73.9		
Deaths due to infectious causes	Yes	8/37	21.6	5/47	10.6		0.23
Neonatal infections with unknown HIV status[d]	Yes	3/54	5.6	0/93	0		0.02

[a] SCBU= Special Care Baby Unit

[b] Among those admitted to SCBU

[c] Wilcoxon test

[d] Neonatal infections and neonatal deaths by infant's birth HIV status among HIV exposed infants only

Table 4

Characteristics of mothers and infants, and early neonatal morbidity and mortality, according to maternal intrapartum antibiotic receipt and, if receipt, type of antibiotics (non-ITT analysis, detailed analysis).

Characteristic or Outcome	Category	Maternal Receipt of Intrapartum Antibiotics						P- value
		Yes: Study Antibiotics (N=866)		Yes: Non-Study Antibiotics (N=167)		No Antibiotics (N=1380)		
MOTHER		n/N	%	n/N	%	n/N	%	
HIV infection Status	Yes	735/855	86	149/165	90.3	1169/1364	85.7	
PROM > 4 hours	Yes	167/825	20.2	50/158	31.6	222/1293	17.2	<0.0001
Clinical chorioaminionitis	Yes	2/162	0.3	2/151	1.3	1/1171	0.2	0.04
Histological chorioamnionitis	Yes	260/725	35.9	53/136	40.4	386/1119	34.5	0.37
INFANT								
Birth weight (g)	Mean	2958		2734		2964		<0.0001
Ballard Score	Mean	38.1		37.1		38.6		<0.0001
Mean Apgar Score	1 minute	8.2		7.8		8.3		0.002
	5 minute	9.6		9.3		9.6		0.07
Infant illness at birth	Yes	82/864	9.5	33/167	19.8	118/1375	8.6	<0.0001
INFANT OUTCOMES								
Admission to SCBU	Yes	80/773	10.3	37/152	24.3	116/1181	9.8	<0.0001
Early neonatal infection	Yes	90/866	10.4	14/167	8.4	137/1375	9.9	0.73
Early neonatal death	Yes	23/866	2.7	14/167	8.4	47/1380	3.4	0.001
Vital status at discharge from SCBU	Dead	20/80	25	10/36	27.8	25/115	21.7	0.71
	Alive & unwell	6/80	7.5	3/36	8.3	5/115	4.3	
	Alive & well	54/80	67.5	23/36	63.9	85/115	73.9	
Deaths due to infectious causes	Yes	6/23	26.1	2/14	14.3	5/47	10.6	0.27
Neonatal infection with respect to HIV status[a]	Unknown	2/4	4.9	1/3	7.7	0/93	0	0.06
	Negative	80/656	12.2	10/124	8.1	107/987	10.8	0.37
	Positive	4/47	8.5	2/14	14.3	13/103	12.6	0.73
Neonatal death with respect to HIV status[a]	Unknown	11/41	26.8	8/13	61.5	30/93	32.3	0.06
	Negative	10/656	1.5	4/124	3.2	9/987	0.9	0.08
	Positive	0/47	0	0/14	0	4/103	3.9	0.30

[a] Neonatal infections and neonatal deaths by infant's birth HIV status among HIV exposed infants only