Syphilis in HIV-infected mothers and infants: Results from the NICHD/ HPTN 040 Study

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BACKGROUND

- Syphilis affects an estimated one million pregnancies per year throughout the world
- 60-90% of pregnant women with untreated primary or secondary syphilis will transmit disease to their infants
- 40% of pregnant women with untreated early syphilis will experience a spontaneous abortion
- Infants with congenital syphilis face a 50% neonatal mortality rate
- Syphilis also increases HIV transmission 2 to 9 fold by increasing viral load, decreasing T cells and interfering with epithelial barriers.

STUDY OBJECTIVES

To evaluate risk factors associated with maternal syphilis as well as factors associated with syphilis and HIV co-infection in infants enrolled in the NICHD/HPTN 040 study.

METHODS

STUDY POPULATION: 1664 mothers and 1684 infants were enrolled in NICHD/HPTN 040 (P1043), a study focused on prevention of *intrapartum* HIV transmission to infants born to HIV-infected mothers who did not receive antiretrovirals prior to labor. Enrollment occurred at 17 sites in Brazil, South Africa, Argentina and the United States.

SYPHILIS DIAGNOSIS: Current maternal infection with syphilis infection was defined as any reactive serological test for syphilis with or without a documented reactive confirmatory test in the absence of documented treatment. A case of congenital syphilis was defined as an infant born to a woman diagnosed with syphilis at the time of delivery or after birth without evidence of treatment >4 weeks prior to delivery. Confirmed cases included those who were diagnosed with syphilis based on abnormal physical exam, or a serum quantitative non-treponemal serologic titer that was fourfold higher than the mother's titer.

HIV DIAGNOSIS: Infants with positive DNA PCR within 48 hours of birth and confirmatory results on repeat testing were classified as having in utero HIV infection. Infants with a negative result at birth and positive results on subsequent testing were classified as acquiring HIV infection during labor.

STATISTICAL ANALYSIS: Univariate and multivariate logistic regression were performed to determine predictors of maternal syphilis and the occurrence of congenital syphilis in their newborns.

IRB APPROVALS: The study was approved by the each site IRB. All analysis were performed using deidentified data.

RESULTS

Figure 1: Algorithm describing HIV infected mothers with positive syphilis serology. Boxes shaded in grey were not included in the sub-analysis.

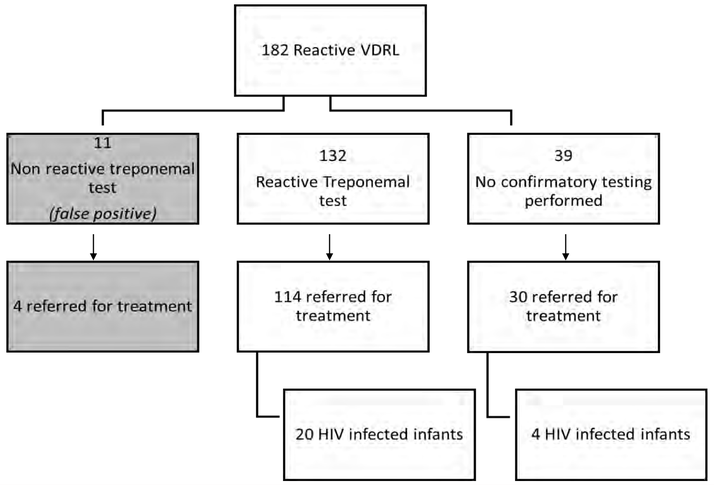

Table 1: Factors associated with maternal positive syphilis status

	Syphilis N=171	No syphilis N=1493	Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)[a]
Age (mean, SD)	28 (±6.3)	27 (±6.3)	1.03 (1-1.1)*	1.03 (1-1.06)*
Ethnicity (non-white)	153 (89%)	1166 (78%)	2.4 (1.4-3.9)*	2.5 (1.5-4.2)*
Illegal substance use (yes)	24 (14%)	123 (8%)	1.8 (1.1-2.9)*	1.5 (0.88-2.7)
Alcohol use (yes)	79 (47%)	511 (35%)	1.6 (1.2-2.3)*	1.5 (1.1-2.1)*
Tobacco use (yes)	61 (36%)	472 (32%)	1.2 (0.87-1.7)	1 (0.67-1.5)
CD4 count (cells/mm^3, SD)	506 (±300)	516 (±310)	1	1
Log_{10} viral load (copies/ml, SD)	9.61 (±2)	9.5 (±1.9)	1.04 (0.96-1.1)	1.01 (0.93-1.1)
Gestational age (mean, SD)	38.5 (±1.7)	38.6 (±1.7)	0.96 (0.87-1)	1
No prenatal Care	76 (45%)	554 (37%)	1.4 (1-2)*	1.5 (0.9-2.12)
Region- (S. Africa)	46 (27%)	420 (28%)	0.9 (0.63-1.3)	0.68 (0.44-1)
HIV transmitted to infant	24 (14%)	116 (8%)	2 (1.2-3.2)*	2.1 (1.3-3.4)*
HIV transmitted in utero	21 (88%)	72 (62%)	4.3 (1.2-15.2)*	

[a] Adjusted for age, ethnicity, tobacco use, illegal drug use, alcohol use, continent of origin, presence of prenatal care, CD4 count and viral load
*P<0.05

Table 2: Symptomatic syphilis cases among newborns enrolled in 040

Case	Mother's VDRL	Confirmatory testing	Country	Infant's titer	Symptoms	Death	HIV Status
1	1:256	Reactive	Brazil	1:256	Premature, low birth weight, pneumonia cardiac arrest	Yes	Unknown
2	1:256	Reactive	South Africa	No titer	Hepatomegaly, sudden death	Yes	Unknown
3	1:64	Reactive	Brazil	1:16	Thrombocytopenia, hepatomegaly	No	Infected in utero
4	Reactive	Not performed	Brazil	No titer	Elevated transaminases, thrombocytopenia, sepsis	No	Infected in utero
5	1:1024	Reactive	Brazil	1:64	Fetal distress, neonatal jaundice, anemia	No	Uninfected
6	Nonreactive	Reactive	Brazil	1:4	Mild rash on extremities	No	Uninfected

Figure 2: Prevalence of maternal syphilis among newly HIV infected pregnant women

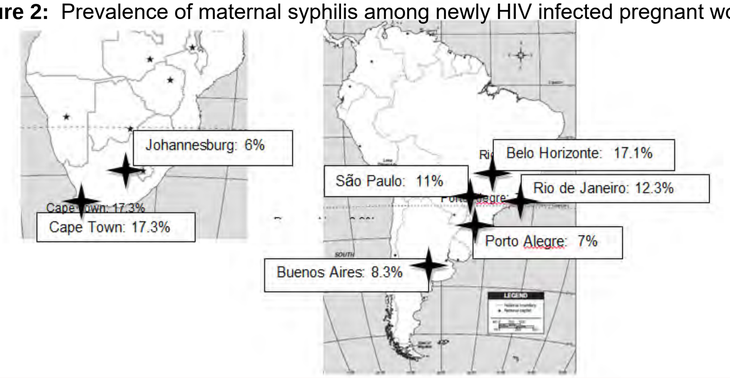

Table 3: Risk factors associated with co-infection in infants

	Co-infected infants (n=24)	Infants not co-infected (n=1660)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Birth weight (mean, SD)	2.735 kg (±430g)	2.991 kg (±522g)	0.99 (0.99-.1)*	1 (0.998-1)
Gestational wk (mean, SD)	38.3 (±2)	38.6 (±1.7)	0.88 (0.71-1.1)	
Maternal VDRL Titers#			3.7 (1.5-9.1)*	3 (1.1-8.2)*
1:1-1:8	12 (52%)	117 (80%)		
≥1:16	11 (48%)	29 (20%)		
Maternal log_{10} viral load	10.8 (±1.6)	9.5 (±2)	1.5 (1.2-1.9)*	1.5 (1.1-1.9)*
HIV Treatment arm			1 (0.44-2.4)	
Zidovudine only	8 (33%)	557 (34 %)		
Two and three drug group	16 (67%)	1103 (66%)		
Delivery type-vaginal	11 (46%)	1073 (65%)	0.45 (0.2-1)	
No use of AZT at delivery	12 (50%)	980 (59%)	0.69 (0.3-1.5)	
Region-S. Africa	3 (13%)	472 (28%)	0.36 (0.11-1.2)	0.3 (0.07-1.1)
Mothers not referred for syphilis treatment	2 (8%)	25 (17%)	.44 (0.1-2)	

*P value <0.05
[a] Adjusted for birthweight, maternal VDRL titers, maternal log_{10} viral load, region

CONCLUSIONS

- Prior studies show that lack of prenatal care, gestational age at the time of syphilis treatment, lower socioeconomic class, multiple sexual partners, and drug use are independently associated with congenital syphilis.
- Our study supports these findings. In addition, alcohol use and non-white ethnicity (likely a marker of social inequality/ lower socioeconomic status) were both associated with increased risk of congenital syphilis in our mainly Brazilian and South African study population (**Table 1**).
- Co-infection with both HIV and Syphilis was associated with: (**Table 1 and 3**)
  - Higher maternal HIV viral loads (AOR 1.5, 95% CI 1.1-19)
  - VDRL titers >1:16 (AOR 3, 95% CI 1.1-8.2)
  - Higher rates of in-utero HIV transmission (AOR 4.3 95% CI1.2-15.2)
- Prompt recognition of syphilis infection in HIV-infected women is necessary to avoid adverse pregnancy outcomes, including HIV *in utero* transmission or fetal/neonatal death.
- While most neonates with congenital syphilis are asymptomatic at birth, symptomatic disease is associated with high morbidity and mortality (**Table 2**)