High rates of adverse birth outcomes in HIV and syphilis co-infected women in Botswana

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Abstract

**Background:** Little is known about the combined impact of HIV/syphilis co-infection on birth outcomes.

**Methods:** Antenatal HIV and syphilis test results, obstetric history, and infant birth outcomes were collected from obstetric records in maternity wards in Botswana between 2008–2011 (5 sites) and 2014–2016 (8 sites). We used logistic regression to compare adverse birth outcomes by HIV and syphilis status. Outcomes included stillbirth, preterm delivery, low birth weight, and in-hospital neonatal death.

**Results:** Of 76,466 women, 75,770 (99.1%) had HIV test results, and 20,520 (27.1%) were HIV positive. Syphilis test results were available for 67,290 (88.0%), and 697 (1.0%) had reactive RPR. Among 692 women with syphilis and an HIV test result, 261 (37.7%) were co-infected. HIV-infected women were more likely to be infected with syphilis than HIV-uninfected women (OR=1.68; 95%CI 1.44–1.96). From 2008–2011 to 2014–2016, the proportion of women with syphilis remained constant (1.1% vs. 1.0%, p=0.41), but HIV/syphilis co-infection declined from 45% to 27% (p<0.0001). Stillbirth occurred in 5.8% of co-infected women, compared with 1.9% with no HIV/syphilis (OR= 3.09; 95% CI1.83–5.23); 3.4% with HIV alone (OR=1.75; 95%CI 1.03–2.97) or 3.7% with syphilis alone (OR=1.58; 95% CI 0.77–3.25). Low birth weight occurred in 24.1% of co-infected women, compared with 12.1% with no HIV/syphilis (OR 2.31; 95 % CI (1.74–3.08); 20% with HIV alone (OR=1.27; 95%CI 0.96–1.69); or 14.6 % with syphilis alone (OR=1.85; 95%CI 1.26–2.74).

All authors declare no conflict of interest exist.
Conclusion: Although HIV/syphilis co-infection in pregnancy has declined in the past decade, co-infection was associated with adverse birth outcomes.

Introduction

Syphilis and HIV present public health challenges that particularly affect resource limited settings including up to 1.4 million pregnant women worldwide [1–7]. Both can be transmitted by mother-to-child transmission during pregnancy and at birth, leading to infection in the infant [4, 8–11]. Maternal infection may also lead to adverse birth outcomes including stillbirth, low birth weight and neonatal death[4, 8, 12–14]. If untreated, greater than 50% of syphilis-affected pregnancies result in adverse events such as mid-late trimester fetal losses, stillbirths, low birth weight, preterm delivery, or congenital syphilis [15–18].

Most African countries have low screening rates for syphilis in pregnancy [7, 17, 19–22]. However, Botswana is one of the few countries with highly prevalent HIV[23] [24] and syphilis [25] [26], with high rates of screening for both, allowing evaluation for risks associated with co-infection. We used data from birth outcomes surveillance performed in 8 healthcare facilities across Botswana to describe syphilis and HIV trends among antenatal women between 2008 and 2016, and their impact on adverse birth outcomes.

Materials and methods

Study population

This was a secondary data analysis of an ongoing birth outcomes surveillance study in Botswana, the “Tsepamo Study”, which aims to study the safety of antiretroviral therapy and HIV on birth outcomes including stillbirth, preterm delivery, SGA and congenital abnormalities[27–30]. Data were abstracted from the maternal obstetric records of all women delivering at government maternity wards during two time periods. From 2008–2011 data were available from 5 sites (Mochudi, Francistown, Kanye, Maun and Ramotswa). From 2014–2016, data were available from 8 surveillance sites. Of the 8 total sites, 2 were at tertiary referral hospitals (Gaborone and Francistown) and the rest were at district or primary hospitals (Ghanzi, Maun, Mahalapye, Molepolole, Selebi-Phikwe and Serowe). Births at these sites were estimated to represent approximately 45% of all births in the country[31].

More than 95% of women in Botswana deliver in a maternity ward and 99.8% have their maternity obstetric card available for data abstraction at the time of discharge from the ward[32]. This study included all pregnant women with data available who attended at least one antenatal visit; had at least one rapid plasma reagin (RPR) test result; and had an HIV test result recorded in pregnancy. Women with multiple pregnancies were excluded from analysis, as were those who delivered before arrival at healthcare facilities or before 24 weeks’ gestation.

All laboratory testing and antenatal visits were performed by Botswana government antenatal care nurses as part of routine care. The services received during the antenatal period include testing for HIV haemoglobin and syphilis. HIV rapid testing is done at the first antenatal visit and repeated at week 36 of gestation and in labor if previous result is HIV
negative[33]. Screening for syphilis through RPR testing is recommended at 2 different time points: at booking/registration for antenatal clinic, and at week 34–36 gestation. Women with a reactive RPR are treated for syphilis with three weekly doses of benzathine penicillin (or with azithromycin/erythromycin in women with penicillin allergy)[33].

Data Collection

De-identified data were abstracted from obstetric cards at the time of discharge from the postnatal wards. Data collected included maternal demographics, medical history, medications administered during the pregnancy, smoking and alcohol use, maternal blood pressure, weight, gestational age at first antenatal care visit, results for HIV testing, RPR and haemoglobin levels. If HIV-infected, the obstetric card captures date of diagnosis, most recent CD4 cell count value and antiretroviral drugs prescribed. For the infant, the obstetric record captures gestational age at delivery, APGAR score, birth weight, length at birth, head circumference, congenital anomalies, and other examination findings at time of birth and discharge.

Exposure Definitions

All women with reactive RPR were considered to be syphilis-infected. Women who received antibiotics in pregnancy, which are known to treat syphilis (penicillin, erythromycin, azithromycin, or ceftriaxone) were considered to be treated. Any positive rapid HIV test or documentation of a prior positive HIV test was considered to indicate HIV infection.

Outcome Definitions

Outcomes were stillbirth, preterm delivery (<37 weeks’ gestational age), low birth weight (<2500g), and in-hospital neonatal death (<28 days). Estimated gestational age was determined at the time of delivery by the government maternity nurses, using last menstrual period as reported by the mother at initial antenatal care visit and/or ultrasound scan in pregnancy when available. Fundal height estimates were rarely used in instances when last menstrual period or ultrasound were not available. Stillbirths included both fresh stillbirths and macerated stillbirths (APGAR 0,0,0). Neonatal death was defined as any death in an infant less than 28 days of life who had not been discharged out of hospital (and therefore could be captured by the in-hospital surveillance).

Statistical Analysis

Statistical analysis was performed using STATA (version 13.0). Frequencies and proportions were used to describe maternal characteristics, HIV and syphilis status and birth outcomes. We used univariate and multivariable logistic regression techniques to describe adverse birth outcomes by HIV and syphilis status. Birth outcomes in HIV syphilis co-infection were also compared with birth outcomes in HIV infection alone and in syphilis infection alone. For the final adjusted model, we included univariate factors p<0.2. We examined effect modification using the Mantel-Haenszel analysis in order to determine the potential interaction of HIV and syphilis on birth outcomes.
Ethical approval

Study approval for the Birth Outcomes Surveillance studies were obtained from the Health and Research Development Committee in the Botswana Ministry of Health and the Office of Human Research Administration in Harvard T. H. Chan School of Public Health.

Results

From 2008–2011 and from 2014–2016, a total of 76,466 women delivered at all the surveillance sites; 31,590 (41.3%) in 2008–2011, and 44,876 (58.7%) 2014–2016. In the two study periods, the median age of the pregnant women was 26 years (interquartile range (IQR) 21 to 31 years). A majority of the women were unmarried (88%) and were educated up to secondary school (70%). About half of the women (53%) were unemployed. There were no significant demographic and/or geographic differences between study periods (data not shown).

Seroprevalence of HIV Infection, syphilis, and Coinfection

HIV test results were available for 75,770 (99.1%) of the pregnant women, and 20,520 (27.1%) were HIV infected. Of the HIV infected participants, 18,741 (91.4%) had received an antiretroviral regimen in pregnancy. Between 2008–2011 and 2014–2016, the proportion of women with HIV decreased, from 29.4% to 25.4% (p<0.00001). Syphilis test results were available for 67,290 (88.0%) women, and 697 (1.0%) had reactive RPR. Between 2008–2011 and 2014–2016, the proportion of women with syphilis remained constant (1.1% vs. 1.0%, p=0.41).

Among only HIV positive women, 261 (1.5%) of 17,806 tested had reactive RPR. Similarly, among 692 women with syphilis who also had an HIV test result, 261 (37.7%) were HIV infected. HIV-infected women were more likely to be infected with syphilis than HIV-uninfected women (OR=1.68; 95%CI 1.44–1.96). The prevalence of HIV/syphilis co-infection declined from 45% between 2008–2011 to 27% between 2014–2016 (p<0.0001).

Adverse Birth Outcomes

Table 2 shows adverse birth outcomes by maternal syphilis and HIV status. Further comparison was also performed with each individual sero-status (syphilis alone or HIV alone). We did not observe any significant effect modification by HIV status (results not shown) in the association between syphilis and birth outcomes.

Stillbirth occurred in 5.8% of co-infected women, compared with 1.9% with no HIV/syphilis (OR= 3.09; 95% CI 1.83–5.23); 3.4% with HIV alone (OR=1.75; 95%CI 1.03–2.97); or 3.7% with syphilis alone (OR=1.58; 95%CI 0.77–3.25).

Low birth weight occurred in 24.1% of co-infected women, compared with 12.1% with no HIV/syphilis (OR 2.31; 95% CI (1.74–3.08); 20% with HIV alone (OR=1.27; 95%CI 0.96–1.69); or 14.6% with syphilis alone (OR=1.85; 95%CI 1.26–2.74).

Preterm delivery was significantly higher in HIV/syphilis co-infected women compared with women with syphilis alone in the adjusted analysis (AOR=1.54; 95%CI 1.05 –2.27).
Delivery of low birth weight infants in HIV/syphilis co-infection was significantly more common compared with syphilis alone (AOR=1.82; 95%CI:1.21–2.75). Neonatal death of babies born to mothers with HIV/syphilis co-infection was not significantly different compared with babies born to women with syphilis alone (AOR=1.71; 95%CI 0.70–4.20).

**Treatment**

Just above half (411/697 or 59.0%) of women with a reactive RPR received antibiotic treatment during pregnancy. The most used antimicrobial was penicillin (47.9%), followed by ceftriaxone (24.7%) and erythromycin (21.1%). Of the 411 participants who were treated for syphilis in pregnancy, 172 (41.3%) had a result for a second RPR test performed during pregnancy; of these women 101 (58.7%) had a negative RPR test.

**Discussion**

We found that while syphilis and HIV co-infection has declined in the past decade, co-infected women had the highest risk for most adverse birth outcomes, compared with uninfected- or single-infected women. Syphilis screening in pregnancy appears to be higher in Botswana (88%) than many other African countries\[16, 18, 34–37\]. The prevalence of syphilis in this population was 1%, and was constant across the two study periods. This is a significantly lower prevalence than reported from studies conducted in Botswana between 2005 and 2006\[25, 26\], and lower than in other African countries in the region\[6, 9, 38\]. This could be because of improved access to health care in the past few decades. These results could also indicate the benefits of HIV prevention and management strategies including early treatment of sexually transmitted infections and safer sex. There is also the possibility of HIV-related mortality having resulted in low prevalence of syphilis, since studies have confirmed a positive correlation between the two\[8, 37\].

HIV prevalence is high in Botswana, particularly among pregnant women\[31, 32, 39\]. In this study we showed a 4% decrease in HIV prevalence among pregnant women between the two study eras, documenting encouraging improvements in HIV prevention (and perhaps the effect of HIV treatment) over time. The 1.3% prevalence of co-infection with syphilis is significantly lower than has been reported in other populations, where about 9.5% of HIV infected adults are known to also have syphilis infection\[40\]. This could be because of the general low syphilis prevalence in the country.

The prevalence of stillbirth was high among HIV and syphilis co-infected women, consistent with existing literature\[8, 12, 19\]. High stillbirth despite high rates of screening could be due to delays in syphilis treatment, or to a lack of treatment effect. Furthermore, co-infected women were more likely to have preterm and low birth weight infants compared with women with syphilis only. The mechanism of the synergistic effect of HIV and syphilis infection on adverse birth outcomes is poorly understood, requiring further study\[12, 41–43\].

This study had a large sample size, making it well powered to reach conclusions despite the relatively low prevalence of syphilis and co-infection. Limitations of our study included reliance on medical record abstraction after delivery (although obstetric cards are generally...
complete). Treatment of syphilis may occur during pregnancy or in the postnatal period depending on when the diagnosis was made. We did not include data about syphilis treatment in the postnatal period. Furthermore, complete syphilis treatment data were only available for 2014–2016 and were not sufficient to make conclusions about the effectiveness and completeness of syphilis treatment in the antenatal period in Botswana. Neonatal deaths in this study were only recorded for infants who had not been discharged from the hospital after birth. This may under-represent neonatal deaths in the population. However, given that most women in Botswana deliver in a healthcare facility, most babies who are not thriving at birth are generally not discharged home. Finally, this was an observational study, so causality of adverse birth outcomes among HIV and syphilis co-infection cannot be established. Observational studies are more prone to bias and confounding but a randomized study is not feasible for this question.

In summary, we have shown a high rate of adverse birth outcomes among HIV/syphilis co-infected mothers and overall decline in HIV/syphilis co-infection. The decline in HIV/syphilis co-infection could be because of widespread availability of antibiotics that treat syphilis, or factors associated with the changing epidemiology of HIV in Botswana. Further studies are warranted to elucidate the mechanism by which HIV and syphilis may increase the rate of adverse birth outcomes.

Acknowledgments

We wish to thank the Botswana Ministry of Health and Study Staff at Botswana Harvard AIDS Institute Partnership. The Tsepamo study was funded by NIH R01HD080471. We also wish to thank Dr Bhekiqiniso Shava for editing the manuscript. ES was partially supported by the Harvard University Centre for AIDS Research (CFAR), an NIH funded program (P30 AI060354), which is supported by the following NIH Co-Funding and Participating Institutes and Centers: NIAID, NCi, NICHD, NIDCR, NHLBI, NIDA, NIMH, NIA, NIDDK, NIGMS, NMHD, FIC, and OAR. SM was partially supported by Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE), a DELTAS Africa Initiative [grant # DEL-15–006]. The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences (AAS)”s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa’s Development Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust [grant #107752/Z/15/Z] and the U.K. government. The views expressed in this publication are those of the authors does not necessarily represent the official views of the National Institutes of Health, AAS, NEPAD Agency, Wellcome Trust, or the U.K. government. The funders had no role in the study design, data collection and decision to publish, or in the preparation of the manuscript

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Table 1:
Characteristics of women who delivered live singleton infants in the two study periods, by HIV and syphilis status

|                        | Total N=76,465 | HIV neg Syph neg N = 48,583 | HIV pos Syph neg N = 17,545 | HIV neg Syph pos N = 431 | HIV pos Syph pos N = 261 |
|------------------------|---------------|-----------------------------|-----------------------------|-------------------------|-------------------------|
| Median Age (Q1, Q3)    | 26 (21, 31)   | 24 (21, 29)                 | 30 (25, 34)                 | 24 (21,30)              | 30 (26, 34)             |
| Married % (n)          | 12 (9,325)    | 13 (6,339)                  | 10 (1,780)                  | 10 (43)                 | 8 (20)                  |
| Unmarried % (n)        | 88 (65,660)   | 87 (41,352)                 | 90 (15,450)                 | 90 (380)                | 92 (229)                |
| Occupation             |               |                             |                             |                         |                         |
| Student % (n)          | 8 (5,764)     | 10 (4,643)                  | 3 (489)                     | 7 (31)                  | 1 (3)                   |
| Unemployed/Housewife % (n) | 53 (40,677) | 52 (25,147) | 54 (9,385) | 59 (253) | 54 (141) |
| Employed % (n)         | 34 (25,789)   | 33 (16,220)                 | 38 (6,677)                  | 28 (119)                | 41 (106)                |
| Unknown % (n)          | 6 (4,233)     | 5 (2,572)                   | 6 (992)                     | 7 (28)                  | 3 (9)                   |
| Educational Status     |               |                             |                             |                         |                         |
| None/Primary % (n)     | 9 (7,214)     | 7 (3,371)                   | 15 (2,545)                  | 10 (43)                 | 19 (50)                 |
| Secondary % (n)        | 70 (53,323)   | 68 (33,088)                 | 73 (12,852)                 | 71 (308)                | 73 (191)                |
| Tertiary % (n)         | 18 (13,748)   | 22 (10,849)                 | 9 (1,610)                   | 17 (73)                 | 5 (13)                  |
| Unknown % (n)          | 3 (2,180)     | 3 (1,274)                   | 3 (538)                     | 2 (7)                   | 3 (7)                   |
| Antiretroviral Therapy (ART) |          |                             |                             |                         |                         |
| On ART if HIV+ % (n)   | 91 (18,743)   | N/A                         | 93 (16,250)                 | N/A                     | 88 (230)                |
| Not on ART if HIV+ % (n) | 9 (1,749)    | N/A                         | 7 (1,268)                   | N/A                     | 11 (30)                 |
| Low maternal haemoglobin <11g/dL % (n) | 38 (27,288) | 33 (15,715) | 48 (8,310) | 33 (140) | 53 (136) |
Table 2:
Adverse Birth Outcomes by Syphilis and HIV Status

| Adverse birth outcome | HIV Syphilis Status | N   | Number with outcome n (%) | Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI) |
|-----------------------|---------------------|-----|---------------------------|---------------------|----------------------------|
| **Stillbirth**         |                     |     |                           |                     |                           |
| HIV-/Syphilis-         | 48 579              | 940 | 19.7                      | 1 (ref)             | 1 (ref)                   |
| HIV-/Syphilis+         | 431                 | 16  | 3.7                       | 1.95 (1.18–3.24)    | 1.96 (1.12–3.44)          |
| HIV+/Syphilis-         | 17 541              | 590 | 3.4                       | 1.76 (1.59–1.96)    | 1.41 (1.24–1.59)          |
| HIV+/Syphilis+         | 261                 | 15  | 5.8                       | 3.09 (1.83–5.23)    | 2.20 (1.19–4.09)          |
| **Preterm Delivery**   |                     |     |                           |                     |                           |
| HIV-/Syphilis-         | 48 579              | 8477| 20.0                      | 1 (ref)             | 1 (ref)                   |
| HIV-/Syphilis+         | 431                 | 95  | 25.6                      | 1.41 (1.11–1.78)    | 1.15 (0.87–1.52)          |
| HIV+/Syphilis-         | 17 541              | 4235| 27.4                      | 1.54 (1.48–1.61)    | 1.40 (1.33–1.48)          |
| HIV+/Syphilis+         | 261                 | 71  | 31.4                      | 1.87 (1.42–2.46)    | 1.49 (1.09–2.05)          |
| **Low Birth weight**   |                     |     |                           |                     |                           |
| HIV-/Syphilis-         | 48 579              | 5857| 12.1                      | 1 (ref)             | 1 (ref)                   |
| HIV-/Syphilis+         | 431                 | 63  | 14.6                      | 1.25 (0.96–1.64)    | 1.27 (0.93–1.73)          |
| HIV+/Syphilis-         | 17 541              | 3507| 20.0                      | 1.82 (1.74–1.91)    | 1.79 (1.69–1.90)          |
| HIV+/Syphilis+         | 261                 | 63  | 24.1                      | 2.31 (1.74–3.08)    | 2.19 (1.58–3.03)          |
| **Neonatal Death**     |                     |     |                           |                     |                           |
| HIV-/Syphilis-         | 48 579              | 520 | 1.1                       | 1 (ref)             | 1 (ref)                   |
| HIV-/Syphilis+         | 431                 | 11  | 2.7                       | 2.47 (1.35–4.51)    | 2.75 (1.45–5.21)          |
| HIV+/Syphilis-         | 17 541              | 251 | 1.5                       | 1.36 (1.17–1.58)    | 1.12 (0.94–1.34)          |
| HIV+/Syphilis+         | 261                 | 4   | 1.6                       | 1.50 (0.56–4.03)    | 1.08 (0.34–3.39)          |
| **Any adverse birth outcome** |     |     |                           |                     |                           |
| HIV-/Syphilis-         | 48 579              | 576 | 1.2                       | 1 (ref)             | 1 (ref)                   |
| HIV-/Syphilis+         | 431                 | 11  | 2.6                       | 2.18 (1.19–3.99)    | 1.97 (0.97–4.00)          |
| HIV+/Syphilis-         | 17 541              | 396 | 2.3                       | 1.92 (1.69–2.19)    | 1.56 (1.34–1.83)          |
| HIV+/Syphilis+         | 261                 | 11  | 4.2                       | 3.67 (1.99–6.75)    | 2.64 (1.29–5.41)          |

* Adjusted for maternal age, marital status, occupation, education, parity.

b Adjusted for maternal age, marital status, occupation, education, parity, low maternal haemoglobin.

c Adjusted for maternal age, occupation, education, parity.

* Any adverse birth outcome refers to a composite value of the birth outcomes (stillbirth, preterm delivery, low birth weight and neonatal death).