Factors associated with delivering premature and/or low birth weight infants among pregnant HIV-positive women on antiretroviral treatment at Dr George Mukhari Hospital, South Africa

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Introduction

An estimated 36.7 million people were living with the human immunodeficiency virus (HIV) worldwide in 2015, of which most (68%) lived in sub-Saharan Africa.1 In South Africa (SA), the national surveillance of HIV and syphilis infection found an HIV prevalence of 29.7% amongst pregnant women in 2013.2 The use of ARV drug exposure, HIV, pregnant women can be identified and have access to treatment during pregnancy. Therefore, this study aimed to evaluate the risk of delivering a premature or LBW infant amongst HIV-positive pregnant women on ART and ARV prophylaxis in our setting.

Methodology

Study design
An observational cross-sectional study was conducted at Dr George Mukhari Hospital (DGMH) for a period of seven months from April to October 2012.

Study settings and population
The hospital is a tertiary academic hospital of the Sefako Makgatho Health Science University previously known as the University of Limpopo (Medunsa Campus). It is located in the north of Pretoria, the capital city of South Africa. Pregnant women with complications are referred to the DGMC from surrounding primary healthcare clinics and a secondary hospital in the area. The hospital services a large community of mostly black African individuals. The data for the study were collected from the postnatal and neonatal wards of this hospital. Mothers with non-complicated vaginal and Caesarean section (CS) deliveries are sent to the postnatal ward with their babies if they are term or preterm with a weight of more than 1 800 g. Preterm babies less than 1 800 g and sick babies are admitted to the neonatal ward. The study included all mother and baby pairs from both the postnatal ward and the neonatal ward.

Background: Prematurity and low birthweight (LBW) deliveries amongst pregnant women infected with the human immunodeficiency virus (HIV) remain a challenge worldwide. The association between prematurity, LBW and antiretroviral therapy (ART) or prophylactic antiretroviral drug (ARV) exposure in pregnancy is unclear. This study evaluates the risk of delivering a premature and/or LBW infant among HIV-positive pregnant women on ART or prophylactic ARV.

Methods: A cross-sectional study was conducted (April to October 2012). HIV-positive women on prophylactic ARV (dual therapy) or lifelong ART (triple therapy or HAART) were enrolled in the study. Women who did not have a documented HIV result during pregnancy, those tested before delivery and those found to be HIV-positive were considered as not exposed to ARV drugs during pregnancy. This group received a standard dose of nevirapine during labour. The control group was made up of HIV-negative women.

Results: Of the 496 mothers enrolled in the study, 59% (288/496) were HIV-positive, of whom 72% (206/288) were on ART or prophylactic ARV. The mean age was 27.6 ± 6.5 years (15 to 47 years). The mean gestational age (GA) was 35.9 ± 3.6 weeks (24–42 weeks). Infants’ birthweights ranged from 550 to 4 900 g (2.5 ± 0.9 kg). HIV-positive mothers not on ART or ARV prophylaxis were likely to deliver an infant at GA < 28 weeks (p < 0.05) or birthweight < 1 000 g (p < 0.05) compared with their counterparts.

Conclusion: HIV-positive pregnant women not on ART or ARV prophylaxis were at a risk of delivering babies at GA < 28 weeks or birthweight < 1 000 g. There is a need to encourage early and regular attendance for antenatal care so that HIV-positive pregnant women can be identified and have access to treatment during pregnancy.
Sampling technique and sample size
A minimum sample size of 322 was calculated based on the 95% confidence level, 5% sampling error and prevalence of HIV amongst pregnant women of 30%.

Exclusion criteria
Pregnant women with a chronic medical condition, such as cardiac disease, epilepsy, renal disease, liver failure, psychiatric condition and diabetes mellitus on treatment before pregnancy, were excluded. We also excluded multiple pregnancies because of the high risk of a premature birth. Infants weighing less than 500 g as per WHO definition of viability or less than 24 weeks gestational age (GA) were also excluded.

Data-collection methods
Data were collected from mothers’ files in the postnatal ward, the antenatal card and from a questionnaire answered verbally by the mothers. The following information was obtained: age, HIV status, CD4 cell count and mode of delivery. The infant’s weight was measured with a mechanical infant scale model RGZ-20 and the gestational age was calculated using the Ballard score. Prematurity was defined as delivery before 37 completed weeks by vaginal delivery or Caesarean section.

A kit for a rapid HIV Elisa test (HIV test first response HIV card test 1–2, Kachigan, Daman, India and Pareekshack HIV Triline card test Bangalore, Karataka, India) was used by nursing staff to test the HIV status of mothers who did test for HIV during pregnancy. The HIV-positive women were then divided into two groups, those who were HIV-positive on ART (triple therapy during pregnancy) or ARV prophylaxis and those who were HIV-positive but not on ART or ARV prophylaxis. The HIV-positive not on ART group was made up of women who tested HIV-positive in the period of the study. Some 2% (9/505) of mothers and their infants were excluded from the study because of a 22% (2/9) chronic medical condition and 78% (7/9) had twin infants. Of the 496 remaining mothers, 41% (208/496) tested HIV-negative, while 59% (288/496) were HIV-positive. Of the HIV-positive mothers, 72% (206/288) were on ART, while 18% (82/288) were not on ART. The ages of the mothers ranged from 15 to 47 years with a mean of 27.6 ± 6.5 years. The mean GA was 35.9 ± 3.6 weeks.

A total of 505 of mother and infant pairs were screened during the period of the study. Some 2% (9/505) of mothers and their infants were excluded from the study because of a 22% (2/9) chronic medical condition and 78% (7/9) had twin infants. Of the 496 remaining mothers, 41% (208/496) tested HIV-negative, while 59% (288/496) were HIV-positive. Of the HIV-positive mothers, 72% (206/288) were on ART, while 18% (82/288) were not on ART. The ages of the mothers ranged from 15 to 47 years with a mean of 27.6 ± 6.5 years. The mean GA was 35.9 ± 3.6 weeks.

Table 1 shows the relationship between maternal HIV status and the infant’s weight, mode of delivery, birthweight and GA. The mean age of HIV-positive mothers on ART or ARV prophylaxis was 26.34 ± 6.93 years, and the mean GA was 35.9 ± 3.6 weeks.

Table 1: General characteristics of enrolled mothers and their infants

| Factor                  | HIV-negative n = 208, n (%) | HIV-positive on ART/ARV prophylaxis n = 206, n (%) | HIV-positive not on ART n = 82, n (%) | p-value |
|-------------------------|-----------------------------|--------------------------------------------------|-------------------------------------|---------|
| Mother’s age (years)    | 26.34 ± 6.93                | 28.63 ± 6.34                                     | 27.76 ± 6.10                       | < 0.0001|
| Delivery by C/S         | 83 (40)                     | 74 (36)                                         | 7 (9)                              | < 0.0001|
| Birthweight             |                             |                                                 |                                     |         |
| < 1 000 grams           | 8 (4)                       | 8 (4)                                           | 10 (12)                            | 0.0190* |
| 1 000–1 499 grams       | 34 (16)                     | 21 (10)                                         | 13 (16)                            | 0.1540  |
| 1 500–2 499 grams       | 37 (18)                     | 52 (25)                                         | 13 (16)                            | 0.0930  |
| ≥ 2500 grams            | 129 (62)                    | 125 (61)                                        | 46 (56)                            | 0.6330  |
| Gestational age         |                             |                                                 |                                     |         |
| < 28 weeks              | 3 (1)                       | 2 (1)                                           | 6 (7)                              | 0.0030  |
| 28–29 weeks             | 9 (4)                       | 13 (6)                                          | 4 (5)                              | 0.6550  |
| 30–36 weeks             | 47 (23)                     | 50 (24)                                         | 22 (27)                            | 0.7480  |
| ≥ 37 weeks              | 149 (72)                    | 138 (67)                                        | 49 (60)                            | 0.1430  |

Notes: Post hoc analysis: HIV –ve vs. HIV +ve on ART, p < 0.05; HIV –ve vs. HIV +ve not on ART, p > 0.05; HIV +ve on ART vs. HIV +ve not on ART, p > 0.05.
*Fisher’s exact test.
significantly higher than the control group ($p < 0.05$). HIV-negative mothers significantly delivered by CS compared with the other groups ($p > 0.05$). The risk of birthweight < 1 000 g was higher (12%) amongst HIV-positive mothers not on ART or ARV prophylaxis compared with HIV-positive mothers on ART or ARV prophylaxis (4%) and (4%) the control group ($p < 0.05$). However, there was no significant difference in infants weighing ≥ 1 000 g among the three groups ($p > 0.05$). A significantly greater proportion (7%) of mothers not on ART or ARV prophylaxis delivered babies at GA < 28 weeks, compared with mothers on ART or ARV prophylaxis (1%) and (1%) the control group ($p < 0.05$).

As seen in Table 2, there was no significant relationship between mode of delivery and mother's age and the gestational age of the infant ($p > 0.05$). Infants delivered by CS had significantly higher mean birthweight than those delivered vaginally (2.68 ± 0.89 vs 2.47 ± 0.91, $p < 0.05$). Few ($n = 86$) of the HIV-positive mothers had a CD4 count cell recorded due to the NHLS change of system to Lab Track, which made it impossible to make a meaningful comparison.

**Discussion**

From our study, 72% of the HIV-positive pregnant mothers were on ART, which was comparable to the rate of 72% found in Kenya$^{12}$ and 82% found in Ghana.$^{13}$ The report by UNAIDS showed that, in 2013, only 68% of HIV-positive pregnant women in sub-Saharan Africa received ART.$^{14}$ Evidently, early initiation of ART or ARV prophylaxis during pregnancy has significant clinical benefits.$^{4,5}$ However, these studies show that the uptake of ART among HIV-positive pregnant women in sub-Saharan Africa remains a challenge and is associated with a shortage of healthcare workers, the poor attitudes of healthcare workers, transport costs and long waiting times.$^{15}$ In the present study, HIV-positive mothers on ART or ARV prophylaxis and HIV-negative mothers had a lower risk of premature birth compared with HIV-positive mothers not on ART or ARV prophylaxis.

Overall, nearly half (41%) of the HIV-positive pregnant women in our study delivered LBW babies, which is slightly higher than the rate of LBW babies (34%) observed in India.$^{16}$ Interestingly, Xiao and co-workers, in their meta-analysis, found that ARV drug usage did not significantly change the association of maternal HIV exposure to ARV drugs with LBW.$^{11}$ In contrast, one study in South Africa found that HIV-positive mothers not on ART or ARV prophylaxis delivered significantly LBW infants compared with the HIV-positive mothers on ART or ARV prophylaxis.$^{17}$ It is worth noting that, in our study, HIV-positive women not on ART or ARV prophylaxis significantly delivered babies with birthweight < 1 000 g. The findings in our study could be due to the fact that the HIV-positive mothers not on ART might have had a lower CD4 cell count and higher HIV RNA viral load, which might have contributed to extremely LBW (< 1 000 g) babies.$^{18}$

In our study, 35% of the HIV-positive pregnant women delivered preterm babies, which is higher than the 11% reported in Nigeria$^{19,20}$ and 25% in India.$^{21}$ The reason for the high premature birth rate in our study is unclear, but it could be related to young age, low education levels, no or low pregnancy weight gain and HIV disease stage 2 or more.$^{22}$ Several studies have shown an association between prematurity, low birthweight and CD4 cell count.$^{17,18}$ In our study, few ($n = 86$) HIV-positive pregnant women had their CD4 cell count documented, which made it impossible to make a meaningful comparison.

With regard to the association between CS and maternal HIV status, our findings show a significantly greater proportion of HIV-negative pregnant women delivered by CS compared with HIV-positive pregnant women on ART or those not on ART.$^{22}$ The obstetric reasons for lower CS rate amongst HIV-positive pregnant women in our study were not documented. However, the 2010 South African National Guidelines on HIV Treatment did not recommend an elective Caesarean for the prevention of mother-to-child transmission (PMTCT).$^{23}$ We found no significant difference in the mean age of HIV-positive mothers on ART or ARV prophylaxis and those not on treatment, which is in agreement with previous studies.$^{7}$

**Study limitations**

The study did not assess other risk factors associated with preterm delivery, such as socio-economic factors, mother’s height, pregnancy-induced hypertension and sexually transmitted disease. The CD4 cell count and the viral load data were missing for most of the HIV-positive women. Few of the HIV-positive mothers had their CD4 count documented, as the NHLS changed its previous electronic results program (DISALAB) to a better computerised program, Hospital Statistics. Because of this changeover, most of the results were missing. We included some of the women on ARV prophylaxis and their babies as exposed to ARV drugs. Lastly, ART drugs were not documented in the admission maternity files, even for those on ARV prophylaxis.

**Conclusion**

The findings of this study show that HIV-positive pregnant women not on ART or ARV prophylaxis were at a high risk of delivering babies at GA < 28 weeks with birthweight < 1 000 g. The first PROMISE study, conducted in 2013, showed a significantly lower early rate of mother-to-child HIV transmission amongst women on lifelong ART/triple therapy (EFV and NVP based) compared with those receiving ARV prophylaxis.$^{24}$ Therefore, since 2013, the World Health Organization (WHO) PMTCT guidelines do not recommend ARV prophylaxis for PMTCT, as was the case in the 2010 WHO PMTCT guidelines. There is a need to encourage early and regular attendance at antenatal care sessions so that HIV-positive pregnant women can be identified and be given access to early treatment and support during pregnancy.

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