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MAJOR ARTICLE

# Maternal Factors Associated With Infant Neurodevelopment in HIV-Exposed Uninfected Infants

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***Background.*** This study evaluated maternal factors associated with infant neurodevelopmental outcomes among HIV-exposed uninfected (HEU) infants in rural South Africa. This study followed pregnant women living with HIV pre- and postpartum and evaluated sociodemographic factors, use of antiretrovirals (ARVs), and mental health factors as predictors of HEU infant developmental outcomes (cognitive, receptive, and expressive communication, fine and gross motor skills).

***Methods.*** Participants were 80 mother–infant dyads. Mothers were assessed during pregnancy, and HEU infant development was assessed at a mean (SD) of 13.36 (1.89) months of age.

***Results.*** Women were an average (SD) of 28.9 (5.2) years of age, and infants were on average 13.4 (1.9) months old. An analysis of covariance indicated that infants whose mothers had ARV detected in dry blood spots at 32 weeks of pregnancy had lower functioning scores in the cognitive domain than those with undetected ARV (n = 14; M, 15.3 vs 17.2; $P = .048$). Antenatal physical intimate partner violence was also associated with delayed cognitive functioning ($F$ (1, 74), 4.96; $P = .029$).

***Conclusions.*** This study found risks for delayed infant cognitive development to be associated with the use of ARV during pregnancy and intimate partner violence, although findings merit replication due to the low sample size. Given the growing number of HEU infants, the necessity to better understand the potential toxicity of ARV exposure in utero is apparent. Similarly, the need for preventing intimate partner violence and screening for, and managing, developmental delays among these infants is increasing.

**Keywords.** antiretrovirals; infant development; pregnancy; South Africa; women.

HIV infection has been associated with developmental delays in children born to mothers living with HIV, and HIV-exposed uninfected (HEU) infants born to HIV-infected mothers have also recently been reported to have cognitive and motor delays despite the use of antiretrovirals (ARVs) to prevent perinatal infections [1–3]. The use of ART pre- and postpartum aims to improve the health of pregnant women and prevent mother-to-child transmission (PMTCT), while minimizing toxicity for both mother and infant. Although the effect of ARV on maternal health and on eliminating HIV transmission is clear, the potential toxicity of ARV in infants has not fully been determined [4–7].

Studies on the effects of the use of ARV during pregnancy suggest that there may be an increased risk of poor developmental outcomes among HEU, but large cohorts and retrospective studies have not found a definite association [8, 9]. Efavirenz (EFV) is one of the most commonly used ARVs in the world, and is it widely used unless contraindicated due to a history of psychiatric disorders [10]. EFV is widely used for PMTCT in South Africa [11], as large epidemiological studies and evaluation of existing PMTCT programs have not confirmed an increase in birth defects that was described in animal studies. EFV use has also been associated with increased risk of adverse neuropsychiatric effects and suicidality among pregnant women, but its association with developmental outcomes has not been examined [12–17].

In addition to the potential impact of maternal use of ARV on infant development, maternal mental health and intimate partner violence (IPV) during pregnancy may also affect cognitive functioning in infants born to mothers living with HIV [18–21].

As most studies have focused on the effect of maternal ARV detected at birth, research is also needed to evaluate the effects of long-term exposure to ARV on infant development, especially in resource-limited settings where monitoring is infrequent [22]. These factors, that is, ARV exposure during breastfeeding

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[23] and the influence of maternal mental health and intimate partner violence on infant development, highlight the need to examine factors occurring during pregnancy that may negatively impact neurodevelopmental outcomes among HEU infants [24].

This study evaluated maternal factors associated with neurodevelopmental outcomes at a mean (SD) of 13.36 (1.89) months of age among HEU infants born to mothers living with HIV in rural South Africa receiving ARV during pregnancy. Results from this study may guide future studies on HIV management pre- and postpartum and the development of pedagogical recommendations for evaluation and management of neurodevelopmental delays in HEU infants in resource-limited settings.

## METHODS

### Participants and Procedures

This study was a substudy of a nested longitudinal randomized controlled trial (number NCT02085356) evaluating the impact of male involvement on PMTCT uptake in rural South Africa. As part of the study design, all women in the study were required to identify a male partner. Details of the design of the study have previously been described [25]. A convenience subsample (n = 80) of mothers enrolled in the main study with a 12-month visit pending were approached and invited to participate with their infants. All women approached agreed to participate. Participants were pregnant mothers living with HIV and their HEU infants. All women included in this study were on ART per country guidelines with a daily combination single pill of EFV, tenofovir, and emtricitabine. Data presented in this manuscript are from a cross-sectional analysis of longitudinal data collected in women during pregnancy and their infants at a mean (SD) of 13.36 (1.89) months of age, who were assessed November 6, 2015, to March 14, 2018. Inclusion criteria included pregnant women with documented HIV infection who reported having a male sexual partner, 20–24 weeks pregnant (typical time of entry into antenatal clinic care), and at least 18 years of age. Exclusion criteria included active psychosis or intoxication.

Women completed interviews in English, Zulu, or Sotho using Audio Computer-Assisted Self-Interview (ACASI) software to minimize bias and accommodate diverse literacy levels. Baseline assessments were completed by mothers at 6–28 weeks of pregnancy (M [SD], 18.1 [5.3] weeks), and

**Table 1. Demographic and Psychosocial Characteristics of Infant–Mother Dyads (n = 80)**

| Characteristic | All | Not EFV-Exposed (n = 14) | EFV-Exposed (n = 66) |
|---|---|---|---|
| Mother | | | |
| Age, mean (SD), y | 28.97 (5.26) | 30.07 (3.05) | 28.74 (5.61) |
| Educational attainment, No. (%) | | | |
| Grade 0–10 | 16 (20.3) | 3 (21.4) | 13 (20.0) |
| Grade 10–11 | 39 (49.4) | 5 (35.7) | 34 (52.3) |
| Grade ≥12 | 24 (30.4) | 6 (42.9) | 18 (27.7) |
| Monthly household income, No. (%) | | | |
| <599 Rand (~$44) | 40 (50.6) | 5 (35.7) | 35 (53.8) |
| ≥600 Rand | 39 (49.5) | 9 (64.3) | 30 (46.2) |
| Relationship status, No. (%) | | | |
| Unmarried, living separately | 43 (54.4) | 9 (64.4) | 34 (52.3) |
| Unmarried, living together | 26 (32.9) | 4 (28.6) | 22 (33.8) |
| Married, mean (SD) | 10 (12.7) | 1 (7.1) | 9 (13.8) |
| Months since HIV diagnosis | 29.27 (35.41) | 25.89 (31.56) | 18.44 (28.47) |
| Months since ART initiation | 19.76 (28.97) | 27.18 (32.52) | 29.72 (36.22) |
| Antenatal depressive symptoms | 11.91 (5.71) | 11.86 (4.50) | 11.92 (5.97) |
| Antenatal psychological IPV | 3.90 (5.39) | 3.57 (3.20) | 3.97 (5.77) |
| Antenatal physical IPV | 1.19 (2.85) | 0.50 (1.34) | 1.34 (3.07) |
| Infant, mean (SD) | | | |
| Age, mo | 13.36 (1.89) | 13.41 (1.16) | 13.34 (2.03) |
| Cognitive | 15.54 (3.44) | 17.43 (3.72) | 15.14 (3.27) |
| Receptive communication | 11.44 (3.13) | 12.14 (3.23) | 11.29 (3.11) |
| Expressive communication | 11.10 (4.27) | 12.29 (4.45) | 10.85 (4.23) |
| Fine motor | 13.16 (3.25) | 14.50 (4.00) | 12.88 (3.03) |
| Gross motor | 14.84 (3.25) | 15.86 (3.57) | 14.62 (3.17) |

Cognitive skills refer to how infants think, react, learn about, and attend to the world around them. Language domains refer to receptive and expressive communication; receptive communication is the recognition of sounds and words, whereas expressive communication refers to the infants' sounds, gestures, and words in response to familiar and novel stimuli. Fine motor skills include muscle control responses, such as eye movement, as well as reaching and grasping for objects. Gross motor control assesses infants' head control and completion of tasks requiring sitting upright and crawling [29].

Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; IPV, intimate partner violence.

infants were assessed at 9–20 months of age (M [SD], 13.4 [1.89] months). Levels of maternal EFV and TDF were assessed at 32 weeks of pregnancy (range, 18–41 weeks; M [SD], 30.0 [4.8] weeks).

### Measures

#### *Baseline*

At baseline, pregnant participants provided demographic information, including age, education, income, relationship status, and time since HIV diagnosis and ART initiation via self-report. As infant cognitive functioning has been shown to be affected by IPV and maternal depression [18, 19], antenatal psychological and physical IPV was assessed with an adapted version of the Conflict Tactics Scale 18 using 2 continuous scores (CTS-18) [26]. Antenatal depressive symptomatology was assessed among pregnant participants with the 10-item Edinburgh Postnatal Depression Scale using the total continuous score [27]. Women endorsing physical IPV and severe depressive symptoms or suicidal ideation were referred for further assessment. Treatment decisions regarding referred women were made by the mental health professionals at the neighboring district hospitals.

#### *32 Weeks of Pregnancy*

Levels of ARVs were assessed in pregnant participants by dried blood spot (DBS) at 32 weeks of pregnancy using liquid chromatography/tandem mass spectrometry, as previously reported [28]. Cutoff values for all ARVs were undetectable if below 0.02 μg/mL and detectable if ≥0.02 μg/mL; values above the cutoff were deemed "detected." ARVs evaluated included EFV and TDF. As EFV has the longest half-life, we choose to define detection of ARV as detection of EFV at 32 weeks.

#### *Twelve Months Postpartum*

The Bayley Scales of Infant Development (BSID-III) [29] screening component of the test was used to assess infant development at age 9–20 months (M [SD], 13.36 [1.89] months) on 5 domains: cognitive (eg, regards objects, responds to novel stimuli, persistent reach), receptive communication (eg, reacts to sound, reacts to voice, responds to name), expressive communication (eg, social smile), fine motor (eg, eyes follow person, ring), and gross motor skills (eg, controls head upright, turns head side to side), with the assessor starting at the age-appropriate point for the test. The assessments were conducted by a Master's-level doctoral candidate in South Africa trained by 2 US clinical psychologists with subsequent oversight. Assessments were recorded and reviewed by the clinical psychologists in the United States. Assessments were also scored by a Master's-level doctoral student on the US team with training on neuropsychological assessment. Interrater reliability between South Africa and US assessors was 95%. Both scorers were blind to the lab findings of the children. The BSID-III has previously been used in South Africa to assess infants at 3, 6, 9, and 12 months of age without adaption or translation due to the nonverbal nature of the assessment [30], and in the current protocol it was administered by a trained assessor fluent in English and local languages. Age-adjusted (scaled scores) scores were dichotomized as competent or at emerging risk/at risk, applying standard cutoffs to estimate the prevalence of delays, as previously described by the Bayley Scales of Infant Development; score means were also presented [29]. Infant HIV status at 12 months of age was confirmed by polymerase chain reaction (PCR) in DBS.

### Statistical Analyses

Univariate statistics, means and standard deviations, were used to describe the sample. Then, to assess the association between detection of ARV and age-adjusted cognitive domain scores while controlling for depressive symptoms and IPV, an analysis of covariance (ANCOVA) was used. The ANCOVA was conducted to test if the difference in infant cognitive functioning by detected ARV remained after controlling for antenatal depressive symptoms and psychological and physical IPV, as both antenatal depression and IPV could contribute to infant development. Although other variables may have been important to include in assessing associations with neurodevelopmental outcomes, the number of variables included in analyses was minimized due to the sample size. To describe the magnitude of this effect, partial $\eta^2$ were used to compare both significant variables in the model, which are especially useful in designs involving covariates [31]. All analyses were performed in SPSS, version 24.

## RESULTS

### Demographic and Psychosocial Characteristics of Infant–Mother Dyads

As noted in Table 1, women were an average (SD) of 29.0 (5.3) years of age, and infants were an average of 13.4 (1.9) months. Half of women (49%) had 10–11 years of education, and 51% had a monthly income of 599 South African Rand (~USD$44) or less. All women had a male partner; 54% were not married or living with a partner. It had been an average (SD) of 29 (35) months since the mothers had been diagnosed with HIV and 20 (29) months since ART initiation. Antenatal depressive symptoms were an average (SD) of 11.91 (5.71), which is above the cutoff for clinically significant depressive symptoms. Antenatal psychological IPV (SD) was 3.90 (5.39), and physical IPV 1.19 (2.85). Infant HIV status by PCR at 12 months showed that all infants were HIV-negative.

### Infant Development Outcomes

Half of the infants were identified as being at emerging risk or at risk for cognitive delay, 35% for delayed receptive communication, and 56% for delayed expressive communication. Two-thirds (61%) of infants were at emerging risk or at risk for delays

in fine motor skills, and 54% were at risk of delayed gross motor skills.

At 32 weeks of pregnancy, 83% (n = 66) had detected EFV, and 84% (n = 67) had detected tenofovir. Eighteen percent of women did not have detected EFV (n = 14), and 16% (n = 17) did not have detected TDF. Approximately half (56%) of women reported psychological IPV, and 23% reported physical IPV; 43% of women reported clinically significant depressive symptoms.

In bivariate comparisons, HEU infants born to mothers with detected ARV had lower cognitive domain scores, in comparison with HEU infants of mothers without detected ARV (M [SD], 15.14 [3.27] vs 17.43 [3.72]; $t(78)$, 2.33; $P$ = .023). There were no differences by detectable levels of ARV in the receptive ($t(78)$, 0.93; $P$ = .356) and expressive ($t(78)$, 1.15; $P$ = .225) language domains, or in the fine ($t(78)$, 1.43; $P$ = .171) and gross ($t(78)$, 1.30; $P$ = .198) motor domains. In bivariate associations, only physical IPV was significantly related to cognitive skills ($r$ = –.243; $P$ = .031); depressive symptoms ($P$ = .841) and psychological IPV were not ($P$ = .802).

The overall ANCOVA model was significant ($F(4, 74)$, 2.57; $P$ = .045; adj. $r^2$ = .075), and there was a significant effect of detected ARV on infant cognitive functioning ($F(1, 74)$, 4.06; $P$ = .048), controlling for antenatal depressive symptoms and psychological and physical IPV. HEU infants of mothers with detected ARV at 32 weeks had lower scores on the cognitive functioning domain than those with undetected ARV (M [SE], 15.26 [0.41] vs 17.22 [0.88]; $P$ = .048). Antenatal physical IPV was related to infant cognitive functioning ($F(1, 74)$, 4.96; $P$ = .029); antenatal psychological IPV ($F(1, 74)$, 1.09; $P$ = .299) and depressive symptoms ($F(1, 74)$, 0.08; $P$ = .780) were not. Both the effects of detected ARV (partial $\eta^2$ = .052) and physical IPV (partial $\eta^2$ = .063) were of similar size in their association with infant cognitive ability. Based on Cohen's guidelines, the effect sizes for both detected ARV and physical IPV represent a "medium" effect [31, 32].

## DISCUSSION

This study examined maternal factors associated with infant development among HEU infants and found that mothers in whom ARV was detected were more likely to have infants with cognitive developmental delays than mothers with undetected ARV. Additionally, this study confirmed a previously reported association between IPV and delayed infant development [18, 19].

ARVs during pregnant are highly effective in preventing mother-to-child transmission and protecting women against HIV disease progression. However, despite efforts to understand if ARVs may contribute to poor birth outcomes, uncertainty remains regarding the effect of in utero exposure to ARVs on neurodevelopment outcomes of HEU infants. Data from large observational studies worldwide suggest that the use of ARV during pregnancy, in particular EFV, is associated with neurologic abnormalities in infancy and childhood [33, 34]. Most of these studies, however, must be interpreted with caution as they have important methodological limitations, including the difficulty of determining the individual effect of different ARVs or other socioeconomic and environmental factors that may affect infant development [2]. The rates of developmental delay among children in SA are high due to other environmental factors that may be independent of HIV.

Most studies of pregnancy outcomes among women living with HIV have focused on adverse events during pregnancy or birth, and few have linked these maternal factors to neurodevelopmental outcomes of HEU children. This study was unique, as detailed neurodevelopmental evaluations in infants a mean (SD) of 13.36 (1.89) months postpartum were conducted and mothers were assessed for mental health and IPV. Infant cognitive assessments are not routinely performed in rural South Africa, and HEU infants may not receive the same level of evaluation as HIV-infected infants. A recent study in South Africa evaluated HEU infant neurodevelopment and found that cumulative maternal HIV viremia may have adversely the affected motor and expressive domains of infant development, but not the cognitive domain [35]. Although there are plans for the South African Department of Health to replace EFV with dolutegravir as a first agent for HIV treatment [36] and there is ongoing research to better understand the effect of ARV on HEU, the use of ARVs such as efavirenz or integrase inhibitors such as dolutegravir for PMTCT remains an area where further research that includes collection of longitudinal data on mothers and infants is needed [7, 10, 37, 38]. In addition, there is a need to establish programs to provide closer follow-up and cognitive evaluation of the vulnerable population of HEU infants. In addition, although IPV has previously been identified as a barrier to PMTCT, this study highlights that it is also a factor associated with delayed infant development [39, 40], which has important implications for promotion of male involvement during pregnancy.

This study has several important limitations, the most important being that (1) despite using a longitudinal design, conducted a cross-sectional analysis of the data; (2) detecting ARV at 32 weeks does not confirm continued exposure throughout the perinatal period; and (3) small sample size. Additionally, levels of viremia of mothers during pregnancy were not available, and it was not possible to assess the association with viremia and infant development scores. Our findings reveal associations that do not imply causality, as additional factors may influence infant development (ie, other infections, metabolic or mental health conditions, poverty). A longitudinal study with a larger sample and a control group is suggested to attempt to replicate study findings. Other maternal and perinatal factors (ie, maternal education or infant feeding) that may possibly

influence neurodevelopmental scores should be accounted for in future studies.

In conclusion, results suggest that HEU infants may present delayed cognitive development that is potentially associated with the use of maternal ARV and/or IPV during pregnancy, highlighting the importance of identifying an optimal ARV combination for pregnant women living with HIV. In addition, study results highlight the importance of early identification of IPV, the need for interventions to decrease IPV, the need for developmental screening among HEU infants, and the development of pedagogical approaches to manage developmental delays in HEU infants.


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