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The effects of *in utero* exposure to antiretroviral therapy (ART) on the language abilities of HIV exposed uninfected infants

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This study investigates the possible effects of *in-utero* antiretroviral therapy (ART) exposure on early language development in HIV exposed uninfected infants. 27 mother-infant pairs consented to the study. Early language development was assessed using the Rossetti Infant Toddler Language Scale. Descriptive statistics were used to describe the caregiver and infant characteristics, as well as the language and communication abilities of infants exposed to *in-utero* ART. T-test statistics compared the early linguistic development of infants conceived while taking efavirenz and infants that were conceived on a nevirapine or protease-inhibitor (PI lopinavir/ritonavir) containing regimen. Similarly, t-tests or ANOVA statistics assessed maternal and infant characteristics associated with total language development. Results obtained in the study revealed no significant differences between the overall language abilities of infants exposed to regimen containing nevirapine or a PI versus regimen that contained efavirenz. The comparison of mean total Rossetti Infant-Toddler Language scores by infant age and maternal and infant characteristics revealed no significant association between variables except for hospitalization. Results obtained suggest that overall language development may not be significantly affected by *in utero* ART exposure however, further research is warranted to assess whether these infants are at an increased risk of late language emergence.

Key words: HIV, *in-utero* antiretroviral therapy exposure, early language development, Rossetti Infant Toddler Language Scale, HIV, HIV exposed uninfected children.

INTRODUCTION

It is estimated that of the 1.1 million babies that are born in South Africa every calendar year, 300,000 are born to HIV positive mothers (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission, 2015). According to the 2010 South African National Antenatal Survey, 30.2% of pregnant women in South

Africa were HIV-positive (Goga et al., 2014). However, maternal antiretroviral therapy (ART) in pregnancy is beneficial and substantially reduces known risks to the mother and her infant (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission, 2015). In 2010, the first national population-based survey of the effect of the South African prevention of mother-to-child HIV transmission (PMTCT) programme on early HIV transmission from mother to child reported an overall transmission rate of 3.5%. When the survey was repeated in 2011, the transmission rate was found to be 2.7% (Goga et al., 2014). Therefore, the overall transmission rate of 3.5% in 2010 and 2.7% in 2011 represent strong progress which would support the efficacy of prevention of mother-to-child HIV transmission (PMTCT) programmes in reducing mother-to-child HIV transmission (MTCT). The success of this programme is further evidenced in a reduction in maternal and under five mortality in South Africa (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission, 2015). In South Africa, the current PMTCT treatment approach was implemented in 2013 and includes initiating ART for all pregnant women, regardless of CD4 count, with a fixed drug combination consisting of efavirenz, emtricitabine and tenofovir. Previously, nevirapine was the preferred non-nucleoside reverse transcriptase inhibitor that was recommended for pregnant women, until April 2012 when it was replaced by efavirenz due to maternal deaths linked to nevirapine toxicity (Pillay and Black, 2012). Efavirenz (EFV) was previously contra-indicated for the use in pregnancy because of teratogenicity concerns linked to four retrospective case reports of neural tube defects in human infants following first trimester exposure to EFV and animal studies showing neural tube defects following first trimester exposure to efavirenz (De Santis et al., 2002; Ford et al., 2011). However, neural tube defects are a relatively common birth defect (with rates as high as 6.1 per 1000 live births), complicating interpretation of these retrospective case reports (De Santis et al., 2002). Rates of any defect among infants exposed to efavirenz in the first trimester are 2.4% (95% CI: 1.5%, 3.6%) which is similar to that of the general population with 3% for the United States and 5.3% in South Africa (Christianson et al., 2006). Owing to the risk to benefit ratio and toxicities of alternative ART options to use in pregnancy, efavirenz is now part of the first line regimen for pregnant women in South Africa (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission, 2015).

There remains uncertainty about the increased risk for birth defects, particularly those that are not present morphologically at birth, and long-term developmental delay following *in-utero* ART exposure (Pillay and Black, 2012). Understanding the potential toxicities of ART following *in utero* exposure allows one to modify the choice of ART and to detect the effects in individual infants early in order to mitigate long-term effects. Language development begins from birth or even sooner (Rossetti, 2001). For the purpose of this study, language is defined as an individual's ability to understand spoken language and to express themselves using either verbal or non-verbal means of communication (Rossetti, 2001). Similarly, communication is defined as the manner in which an individual conveys and receives a message via verbal and nonverbal modes (Rossetti, 2001; Saxton, 2010). The adequate formation of complex neural pathways within the language centres of the foetal brain during intra-uterine development form the foundation for future language emergence (Saxton, 2010; Owens et al., 2015: Slater, 2007). The adverse effects of *in utero* ART exposure have not been sufficiently explored in the area of language development. This study investigated the language development of HIV-exposed, but uninfected infants in South Africa that were exposed to either efavirenz or nevirapine containing ART regimens *in utero*.

MATERIALS AND METHODS

Study design and participants

Data are presented from a prospective cohort of infants, nested within a larger cohort study of HIV positive, reproductive-aged women on ART followed for pregnancy incidence over 12 months or through six weeks postpartum if conception occurred (Schwartz et al., 2012). Of the 850 women from the original cohort, there were 170 pregnancies among 161 women, including 95 who conceived on nevirapine (NVP) (59.0%), 55 who conceived on EFV (34.2%), and 11 who conceived on a protease inhibitor (6.8%). Pregnancy outcomes were as follows: Lived birth (n=85), voluntary termination of pregnancy (n=44), spontaneous abortion (n=28), ectopic pregnancy and termination (n=5), stillbirth (n=2) and unknown (n=6). Of the 85 known live births, 50 qualified for the study and 27 mother-infant pairs (54.0%) consented for the study.

Data collection and analyses

Mother-infant pairs were invited for the language development sub-study from July to September 2011. Women in the parent cohort were recruited between August 2009 and January 2011 from one of four ART clinics within the inner city of Johannesburg. The adult ART regimen at the time included stavudine, lamivudine, and nevirapine or efavirenz as first line option with lopinovir/ritonavir, zidovudine and didanosine for people who had failed first line therapy. Individual drug substitutions for toxicity could be provided. HIV-infected mothers with a CD4 count ≤200 cells/μL were qualified for ART initiation until April 2010, at which time the guidelines

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were extended to initiate people with tuberculosis or pregnant women with a CD4 count ≤350 cells/µL (Evian, 2007). Women who conceived and delivered a live infant were contacted by a field worker they were familiar with and invited to participate with their infant in the infant language development sub-study. Infants were eligible if they were HIV negative, medically stable, alert and responsive, and between 7 to 18 months of age. The age range was chosen as this age is considered critical for language development. Infants were characterised as being exposed to either efavirenz, nevirapine or lopinavir/ritonavir (Pillay and Black, 2012). The researcher completing the questionnaire and evaluating the infant was kept blinded to the exposure group of the infant.

Mothers were interviewed using a questionnaire that was adapted from the caregiver tool from the Preschool Language Scales 4th Edition (PLS-4) (2009) (Zimmerman et al., 2011). The questionnaire was utilized to determine the mother's and child's demographic information, pregnancy, labour and delivery experience, areas of expressive and receptive language, as well as areas of cognition and attachment. During the interview the researcher observed and recorded the infant's behaviour and the interaction between the caregiver and the infant.

The infants' language development was assessed using the Rossetti Infant-Toddler Language Scale (Rossetti, 2006) as it is suitable to assesses the language skills of children from birth through three years of age. The Rossetti scale evaluates preverbal and verbal areas of communication and interaction by direct observation and caregiver report. Areas that were assessed included: Interaction-attachment, pragmatics, gesture, play, language comprehension, and language expression (Rossetti, 2006). The examiner, a speech-language pathologist and audiologist, established both a baseline and a ceiling for the infant's developmental age by observing, eliciting, or using a caregiver's report of various behaviours listed in each of the six developmental areas. Scores were awarded as follows; 0 = behaviour absent; 1 = behaviour observed; 2 = behaviour could be elicited by the researcher or the mother; 3 = behaviour occurred spontaneously at any given time during the assessment session. Mothers were instructed to neither intervene in testing nor prompt the child unless the researcher requested her assistance.

Data were analysed using Stata 14 (College Station, Texas). Descriptive statistics were used to describe the caregiver and infant characteristics, as well as the language and communication abilities of infants exposed to *in-utero* ART. T-test statistics compared the early linguistic development of infants conceived while taking efavirenz and infants that were conceived on a nevirapine or protease-inhibitor (PI, lopinavir/ritonavir) containing regimen. Similarly, t-tests or ANOVA statistics assessed maternal and infant characteristics associated with total language development scores or protease-inhibitor (lopinavir/ritonavir).

This study was approved by the University of the Witwatersrand Human research Ethics Committee; study protocol number (M110350). All mothers with eligible infants were verbally informed about the scope of the study and invited to participate in the study. Mothers provided written informed consent for themselves and their infants to participate in the study. Any infants identified with psychosocial concerns or neurodevelopmental delay were referred for further management.

RESULTS

Participant characteristics

Among the 27 infants included, 16 mothers were taking a NVP-based regimen during pregnancy (59.3%), 10 mothers were taking an EFV-based regimen (33.3%) and mothers on a protease inhibitor-based regimen (7.4%) at the time they conceived. The mean age of the children examined was 8.3 months (SD 1.7, range 8-12). Table 1 depicts the maternal and infant characteristics of participants.

Language abilities of all infants exposed to ART *in utero*

The language abilities of all infants exposed to ART *in utero* are depicted in Table 2. The evaluation of language abilities for interaction and attachment resulted in a mean score of 10.42 (SD 3.36). For pragmatics, which refers to the use of language in social contexts and the ways in which language is produced and comprehended through language, the mean score was 6.57 (SD 3.05). The mean interaction attachment and pragmatics scores fall within the average range. On evaluating play and language comprehension, the mean scores were 13.63 (SD 5.29) and 17.7 (SD 6.67) respectively. When considering the possible range of scores on the play sub-scale, results obtained indicated mild delay in this area while in the area of language comprehension results indicated average performance. Language expression scored 11.19 (SD 5.60) shows a moderate delay for the expected age range.

Figure 1 compares language abilities of infants exposed *in utero* during the first trimester to EFV versus NVP or a PI. Results obtained for interaction attachment revealed a mean score of 8.3 (SD 2.7) in children exposed to EFV *in utero* and a mean score of 12.0 (SD 0.0) in children exposed to NVP/Protease Inhibitors *in utero* (p=0.169). Infants exposed to EFV *in utero* obtained a mean of 4.6 (SD 2.3) in the area of pragmatics, while children exposed to NVP/PI *in utero* obtained a mean of 8.0 (SD 0.5) in the area of pragmatics (p=0.168). A mean score in the area of interaction attachment and pragmatics could only be obtained for seven (n=7) of the 27 infants as these questions could only be administered to infants 9 months and older. In the area of play, infants exposed to EFV *in utero* obtained a mean score of 14.2 (SD 1.8) and infants exposed to NVP/PI *in utero* obtained a mean score of 13.3 (5.2) (p=0.689). In the area of language comprehension, infants exposed to EFV *in utero* obtained a mean score of 16.6 (SD 2.3) and infants exposed to NVP/PI obtained a mean of 18.3 (SD 15.0) (p=0.537). Finally, infants exposed to EFV *in utero* obtained a mean score of 10.44 (SD 1.63) and infants exposed to NVP/PI obtained a mean of 11.56 (SD 1.4) in the area of language expression (p=0.636).

The total mean score combined for 6 to 8 month old infants exposed to EFV *in utero* was 47.50, while 6 to 8 month old infants exposed to NVP/PI obtained a mean of 40.79 (p=0.324). The total language scores combined for infants 9 to 12 months exposed to EFV *in utero* obtained a mean of 41.67 versus infants exposed to NVP/PI *in*

Table 1. Maternal and infant characteristics of participants.

Characteristic	Value
Maternal characteristics (n=27)	
Age at child's birth, median years (IQR)	31 [28-34]
Number of children, median (IQR)	2 [1-3]
CD4 count prior to delivery, median (IQR)	343 [185-535]
Viral load at time of pregnancy, n (%)	
Virally suppressed	17 (68)
Detectable	8 (32)
ART regimen at time of pregnancy (NNRTI/PI drug), n(%)	
Nevirapine	16 (59)
Efavirenz	9 (33)
PI	2 (7)
Infant characteristics	
Sex, n (%)	
Female	15 (56)
Male	12 (44)
Birth weight, median grams (IQR)	2800 [2400-3200]
Age at time of language development assessment, n (%)	
6-9 months	20 (7%)
9-12 months	7 (26)
Completed 6 week ART prophylaxis regimen after birth, n (%)	25 (93)
Hospitalized after birth, n (%)	4 (15)

IQR = Interquartile range; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

Table 2. Descriptive statistics of the language abilities of all the infants exposed to ART *in utero* using the Rossetti infant-toddler language scale (n=27).

Task	Range of potential score	Mean	SD	Severity rating
Interaction attachment*	0-12	10.42	3.36	Average
Pragmatics*	0-9	6.57	3.05	Average
Play	0-18	13.63	5.29	Mild
Language comprehension	0-36	17.7	6.67	Average
Language expression	0-21	11.19	5.60	Moderate

Language abilities of infants exposed to first trimester EFV compared to infants exposed to first trimester NVP/PI in utero.

utero which obtained a mean of 71.50 (p=0.123).

Overall, results obtained for infants exposed to NVP/PI *in utero* revealed a slightly larger magnitude of effect than results obtained for infants exposed to EFV *in utero* in the language areas of interaction attachment, pragmatics, language comprehension and language expression, however results were not significantly different across groups. Results obtained in the area of play, revealed a slightly larger magnitude of effect in infants exposed to EFV *in utero* as compared to infants exposed to NVP/PI in utero, however again these results were not statistically significantly different across both groups.

Infants that were assessed at 6 to 9 months that had reportedly been hospitalized after birth obtained a mean total language development score of 24.5 (SD 34.6) and infants that had been assessed at 9 to 12 months that had reportedly been hospitalized after birth, obtained a mean total language development score of 29.5 (SD 33.2) (Table 3). In comparison, infants that had not been hospitalized after birth that were assessed at 6 to 9 months obtained a mean total language development score of 44.8 (SD 9.6) and infants assessed at 9 to 12 months obtained a mean score of 70.4 (SD 8.0). There were statistically significant differences between the means of these two groups which suggests that infants that had been hospitalized after birth were at a

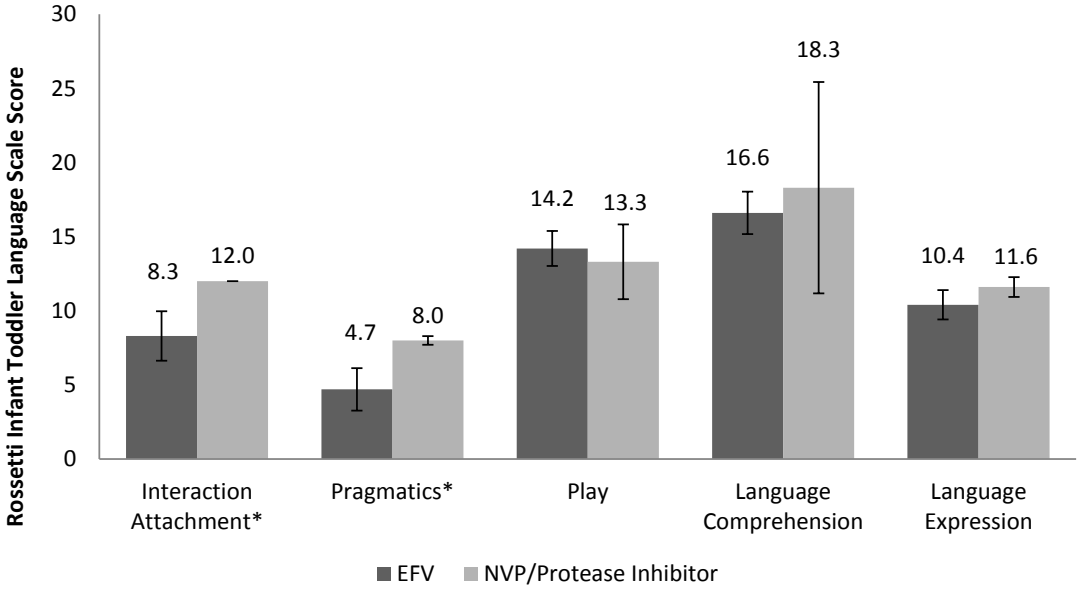

Figure 1. Rossetti infant toddler language scale of infants exposed to first trimester efavirenz and nevirapine or protease inhibitor (lopinavir/ritonavir) *in utero*.

Table 3. Mean total infant Rossetti Infant-Toddler Language Scores by infant age and maternal and infant characteristics.

Characteristic	Infant assessed at 6 to <9 months (n=20); Potential range 0-75.		Infant assessed at ≥9 to 12 months (n=7); Potential range 0-96	
	Mean (sd)	p-Value	Mean (sd)	p-Value
Maternal				
Age		0.228		0.746
<30 years	38.7 (18.0)		54.7 (42.1)	
≥30 years	46.2 (8.0)		61.8 (6.1)	
ART regimen at time of pregnancy (NNRTI/PI drug)		0.224		0.123
Nevirapine	38.7 (15.9)		71.5 (8.8)	
Efavirenz	47.5 (5.0)		41.7 (31.6)	
Protease Inhibitor	53.5 (6.4)		--	
Infant				
Sex		0.569		0.746
Female	41.3 (15.3)		54.7 (42.1)	
Male	45 (11.2)		61.8 (6.1)	
Hospitalized after birth		0.041		0.031
Yes	24.5 (34.6)		29.5 (33.2)	
No	44.8 (9.6)		70.4 (8.0)	

disadvantage in comparison to their non-hospitalized peers.

DISCUSSION

Results obtained in this study revealed no significant differences between the overall language abilities of infants exposed to regimen containing NVP or a PI versus regimen that contained EFV. The results obtained for infants exposed to NVP/PI *in utero* revealed a slightly larger magnitude of effect than results obtained for infants exposed to EFV *in utero* in the language areas of interaction attachment, pragmatics and language comprehension, however results were not significantly different across groups. Results obtained in the area of

play and language expression, revealed a slightly larger magnitude of effect in infants exposed to EFV *in utero* as compared to infants exposed to NVP/PI in utero, however again these results were not statistically significantly different across both groups. Hence results obtained in this study suggest that further research is warranted in a larger study population to assess whether infants exposed to ART *in utero* are at an increased risk of late language emergence as compared to the general South African population. The results lend plausibility to the hypothesis that language development may be impacted by *in utero* ART exposure. A study conducted by Rice et al. (2012a) investigated the association between *in utero* ART exposure with late language emergence in HIV-uninfected, exposed children and found that infants born to mothers with HIV infection and *in utero* ART exposure are at a higher risk of late language emergence than the general population (Rice et al., 2012b).

A subsequent study found that children who were exposed to any ART *in utero* did not have lower mental and psychomotor Developmental Index and Psychomotor Developmental Index scores than unexposed children (Smith et al., 2008). The comparison of mean total Rossetti Infant-Toddler Language scores by infant age and maternal and infant characteristics revealed no significant association between variables except for hospitalization. Results suggest that infants that had been hospitalized after birth were at a disadvantage and at higher risk for late language emergence in comparison to their non-hospitalized peers. This finding is supported by a study conducted by Prothe (2012) which highlights the increased risk of late language emergence in hospitalized infants.

This study had some limitations but these were managed as explained. The sample sizes for the two groups were small and limited the ability to compare differences across groups and to control confounding factors. Nevertheless, there is a lack of data on language development among HIV and ART exposed infants in Africa and this study provides initial data towards understanding language development in this context. The Rossetti Infant Toddler Language Scale is a criterion-referenced scale is not normed on the South African population. However, the use of the Rossetti was efficient in terms of costs and time, and could be performed and completed on infants who had come to the clinic for other routine medical check-ups. Furthermore, the results were interpreted with caution. Though the caregiver questionnaire served to provide supplementary information about the child's language abilities, more information could have been collated using probing questions about parenting capacity and environmental factors. Lastly, the assessment of language development was cross sectional; it is important to also generate information about the sustained effects of ART exposure on child language development over time. Whether language abilities among HIV exposed, uninfected infants improve, plateau or regress over time is unknown.

Despite the aforementioned limitations, given the dearth of data on the relationship between ART and language development, the study results provide important exploratory analyses that could be further researched in a larger study population. More studies are required to further substantiate which independent variables (from the child's developmental needs, parenting capacity and family and environmental factors) influence the language abilities of HIV-negative infants born to mothers with HIV infection who were receiving ART preconception.

In conclusion, the early identification of possible risks to early language development including the identification of possible language delays is vital, as communication difficulties can have devastating effects on the quality of an individual's personal, vocational and cultural environment. The largest part of brain development occurs within the first three years of a child's life (Smith et al., 2008), hence these early years of a child's neurodevelopment are critical for the acquisition of language. Early identification of abnormal early language development is vital for intervention to be maximized. It is essential therefore for healthcare professionals to be aware of possible threats to the speech and language development of this already at-risk population.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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