The Impact of In-utero Antiretroviral Therapy (HAART) Exposure on Infant Outcomes in Johannesburg, South Africa

Karin van der Merwe[1,2], Matthew Chersich[3,1,4,6], Vivian Black[3,1], Karl Technau[1,2], Helen Rees[3,1,5], Ashraf Coovadia[2,1]

1 University of the Witwatersrand, Johannesburg
2 Enhancing Childhood HIV Outcomes, Johannesburg
3 Reproductive Health and HIV Research Unit, Johannesburg
4 International Centre for Reproductive Health, Kenya
5 London School of Hygiene and Tropical Medicine
6 University of Gent, Belgium

BACKGROUND

The Fact:

- The HIV epidemic in South Africa remains one of the fastest growing in the world.
- In Gauteng Province about one third of all women attending antenatal clinics are HIV seropositive[1].
- AIDS is the leading cause of maternal mortality in South Africa[2].
- Use of triple-combination antiretroviral regimens (HAART) in HIV-infected pregnant women has been shown to decrease mother-to-child transmission of HIV (MTCT)[3].
- HAART use in pregnancy reduces maternal morbidity and mortality with consequent benefits for infants, but concerns remain about potential effects of in utero exposure to HAART[4].

The Question:

What are the effects of HAART exposure on foetal development?

AIM

We investigated the impact of HAART exposure on birth weight and gestational age among infants born to South African women with advanced HIV disease.

Table 1: Major studies showing a link between preterm birth or low birth weight and HAART exposure:

Study	Year of Publication	Population	Findings
European Collaborative and Swiss Mother and child HIV cohort study[5]	1998	3920 mother-child pairs in Europe	Protease inhibitor exposure linked with preterm birth
European Collaborative study[6]	2004	4372 live births in Europe	ART-initiation pre-pregnancy associated with preterm birth especially extreme preterm birth
Miami study, Cotter et al[7]	2006	1337 women in Miami	Protease inhibitor exposure associated with preterm birth
National Population-based surveillance study, Townsend at al[8]	2007	4445 pregnancies in UK and Ireland	HAART exposure associated with preterm birth especially extreme preterm birth

Table 2: Major studies showing no link between preterm birth or low birth weight and HAART exposure:

Study	Year of Publication	Population	Findings
US combined cohort[9]	2002	3266 women in the US	No association between LBW or preterm birth and HAART exposure
WITS[10]	2005	2543 women in the US	Preterm birth decreased in association with HAART exposure
Szyld et al[11]	2006	681 women in Latin America and the Caribbean	PI-exposure not significantly associated with LBW or preterm birth compared to NNRTI exposure
Paediatric Spectrum of Diseases[12]	2007	11 321 infants in the US	HAART not significantly associated with preterm birth

METHODS

- 1630 women with advanced HIV attending antenatal antiretroviral clinics in Johannesburg between April 2004 and July 2008 were included.
- All women had CD4 <250cells/mm3
- Gestation and birth weight of infants were compared for
  - HAART-exposed versus HAART-unexposed
  - HAART-exposed, early (<28 weeks gestation) versus late (≥28 weeks)
  - PI-based versus NVP-based and EFV-based HAART exposure for early and late HAART in turn.

RESULTS

Median CD4 counts for mother's of HAART-exposed and unexposed infants were 154 cells/mm3 (IQR101-195) and 191 cells/mm3 (IQR136-220) respectively (P<0.001). Both groups were similar for risk of adverse infant outcomes in terms of smoking, alcohol use, hypertension, diabetes, anaemia, syphilis serology and history of previous miscarriage. HAART-exposed women had a higher rate of previous preterm infant (11%) than the unexposed group (6%, P=0.055).

Table 3: Infant outcomes in women exposed and unexposed to HAART and by duration of exposure

Variables	HAART-unexposed A N=233	HAART-exposed B N=1397	P value (Avs B)	Early HAART-exposed C N=533	Late HAART-exposed D N=427	P value (C vs D)
Time received HAART Median weeks (IQR)		N=921 9.7 (5.0 - 17.6)		N=412 18.4 (12.1-42.6)	N=416 5.8 (3.3-8.5)	<0.001
Gestation: n (%)	N=147	N=946		N=389	N=427	
Extremely preterm	6 (4%)	58 (6%)		40 (10%)	3 (1%)	
Preterm	1 (1%)	80 (8%)		41 (11%)	18 (4%)	
Term/Postdates	140 (95%)	808 (85%)	0.002	308 (79%)	406 (95%)	<0.001
Birth weight (kg): n (%)	N=224	N=1003		N=388	N=407	
Mean (SD)	2.8 (0.6)	2.9 (0.6)	0.008	2.9 (0.6)	2.9 (0.5)	0.39
0.75-1.49	10 (4%)	16 (2%)		8 (2%)	2 (0%)	
1.5-2.49	50 (22%)	199 (20%)		82 (21%)	74 (18%)	
>2.5	164 (73%)	789 (79%)	0.015	298 (77%)	331 (81%)	0.071

Table 4: Infant outcomes in women receiving different antiretroviral regimens and by duration of exposure

Variables	Early HAART - exposed			P	Late HAART - exposed			P
	PI-based ART	NVP-based ART	EFV-based ART		PI-based ART	NVP-based ART	EFV-based ART	
Time taking HAART Median weeks (IQR)	N=139 17.1 (13.7-23.1)	N=192 15.6 (10.7-25.8)	N=81 62.7 (33.1-86.4)	<0.001	N=290 6.1 (3.3-8.7)	N=107 5.1 (3.0-7.8)	N=19 5.2 (3.9-9.4)	0.38
Gestation: n (%)	N=131	N=167	N=91		N=290	N=116	N=21	
Extremely preterm	13 (10%)	15 (9%)	12 (13%)		0 (0%)	3 (3%)	0 (0%)	
Preterm	6 (5%)	25 (15%)	10 (11%)		9 (3%)	8 (7%)	1 (5%)	
Term/Postdates	112 (86%)	127 (76%)	69 (76%)	0.048	281 (97%)	105 (91%)	20 (95%	0.024
Birth weight (kg): n (%)	N=135	N=158	N=95		N=284	N=103	N=20	
Mean (SD)	3.0 (0.6)	2.9 (0.5)	2.7 (0.6)	0.002	2.9 (0.5)	2.9 (0.5)	2.8 (0.5)	0.59
0.75-1.49	5 (4%)	0 (0%)	3 (3%)		2 (1%)	0 (0%)	0 (0%)	
1.5-2.49	18 (13%)	31 (20%)	33 (35%)		46 (16%)	23 (22%)	5 (25%)	
>2.5	112 (83%)	127 (80%)	59 (62%)	<0.001	236 (83%)	80 (78%)	15 (75%)	0.50

CONCLUSION

Among women with advanced HIV disease, HAART exposure to any regimen was associated with preterm birth and this was especially true for HAART-exposure before 28 weeks gestation. HAART exposure did not increase the risk of birth before 34 weeks gestation.

LBW and ELBW were not associated with HAART-exposure; in fact HAART-unexposed women were more likely to deliver LBW infants. One reason for this could be that untreated HIV-infected women with low CD4 counts are at risk to deliver small for gestational age infants.

Contrary to some previous literature, PI-based HAART was not a risk factor for preterm birth or LBW. Early EFV and NVP exposure were most associated with preterm birth. Early EFV-exposure was also associated with LBW compared to other regimens. This could be confounded by higher levels of TB among these women. EFV use in pregnancy is frequently used in the presence of TB co-infection and TB is a risk factor for preterm birth and low birth weight.

Our Answer:

Use of HAART in pregnant women with advanced HIV is associated with delivery of preterm infants between 34 and 37 weeks gestation. Protease inhibitors did not increase the risk and can be used in PMTCT regimens in South Africa.

NOMENCLATURE:

Preterm	Infant born before 37 completed weeks of pregnancy
Extremely Preterm	Infant born before 34 completed weeks of pregnancy
LBW	Low Birth Weight. Infant; weighing less than 2500g at birth
ELBW	Extremely Low Birth Weight. Infant; weighing less than 1500g at birth
NVP	Nevirapine
PI	Protease Inhibitor
EFV	Efavirenz
SD	Standard deviation
IQR	Inter quartile range

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