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Virologic Response To Efavirenz-based First-line In Children By PMTCT Exposure Status

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Background

- WHO recommends an efavirenz (EFV)-based first-line regimen for children ≥3 years starting antiretroviral therapy (ART), despite risks of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance with prevention of mother-to-child transmission (PMTCT) exposure.
- We aimed to investigate the association between PMTCT exposure and virologic outcomes in children ≥3 years starting EFV-based ART using routine data from the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA).

Methods

- Data came from the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration, a regional collaboration of adult and pediatric HIV care and treatment programs.
- We included children aged 3-13 years who initiated EFV-based ART between 2004 and 2014, and had ≥2 viral load (VL) from 4-18 months on ART at 10 IeDEA public sector ART programs in South Africa.
- PMTCT exposure status was recorded by the program at enrolment as exposed, unexposed or unknown. Exact PMTCT regimens were not routinely recorded but maternal and child PMTCT regimens over the study period are shown in tables 1a and 1b.
- We used logistic regression to examine the association between recorded PMTCT exposure and VL >1000 copies/ml (cpm) between 6-18 months on ART adjusting for patient characteristics associated with viral outcomes and calendar year.
- In additional analyses we assumed PMTCT exposure for those where exposure was unknown as either: (1) all exposed as per South African PMTCT guidelines at the time of the child's birth or (2) all unexposed.

Table 1a Maternal PMTCT guidelines over study period

Time period	Regimen
< Jan 1999	No PMTCT
Feb 2002- Feb 2008	NVPSD
2004 onwards	CD4- and clinically-based ART indications
Feb 2008	AZT from 28 weeks; SD NVP
April 2010	AZT from 14 weeks. Truvada and SD NVP
April 2013 onwards	Efavirenz-emtricitabine-tenofovir

Table 1b Infant PMTCT guidelines over study period

Time period	Regimen
< Jan 1999	No PMTCT
Feb 2002- Feb 2008	NVPSD
Feb 2008-March 2010	SDNVP plus AZT
April 2010 onwards	Daily NVP at least 6 weeks

These tables reflect the National Department of Health guidelines over the study period. Differences in guidelines implemented in the Western Cape are accounted for in the assumptions made for outcomes.

Results

- The median age at ART start of 7,896 children included was 7.5 years; 50% girls (Table 2).
- Recorded PMTCT exposure was: 68% unexposed, 7% exposed and 26% unknown.
- VL >1000 cps/ml was experienced by 16.8% of children.
- Children with PMTCT exposure had similar risk of VL >1000 cps/ml compared to unexposed children (adjusted Odds Ratio [aOR]: 1.15; 95% CI:0.80, 1.66), but children with unknown PMTCT exposure were less likely to have VL >1000 cps/ml (aOR: 0.73; 95% CI:0.61, 0.89) (Table 3).
- After assuming children with unknown exposure received PMTCT available according to South African guidelines, there was a similar risk of VL >1000 cps/ml in PMTCT exposed compared to unexposed children (aOR:0.86; 95%CI: 0.69, 1.08).
- When assuming no PMTCT exposure for those with unknown exposure, PMTCT was not associated with VL >1000 cps/ml. Children with WHO-defined immunosuppression had a higher risk of VL >1000 cps/ml (Table 3 and figure 1 &2). Children born between 2006 and 2009 had a higher risk of VL > 1000 cps/ml.

Table 2: Baseline table with "unknown" category allocated to PMTCT according to National Guidelines at date of birth (DoB) and to not receiving PMTCT

	Unknown PMTCT allocated to PMTCT exposure according to DoB			Unknown PMTCT allocated to no PMTCT exposure		
	No (N=6483)	Yes (N=1413)	Total (7896)	No (N=7372)	Yes (N=524)	Total (7896)
Gender						
Female	3283 (50.6)	682 (48.3)	3965 (50.2)	3706 (50.3)	259 (49.4)	3965 (50.2)
WHO Stage						
Stages 1&2	1472 (35.2)	208 (23.4)	1680 (33.1)	1650 (34.0)	30 (13.5)	1680 (33.1)
Stages 3&4	2711 (64.8)	681 (76.6)	3392 (66.9)	3200 (66.0)	192 (86.5)	3392 (66.9)
Immunosuppression						
No	4173 (82.6)	1018 (86.9)	5191 (83.4)	4804 (83.0)	387 (88.0)	5191 (83.4)
Yes	880 (17.4)	154 (13.1)	1034 (16.6)	981 (17.0)	53 (12.1)	1034 (16.6)
Year of ART start						
2004-2005	979 (15.1)	75 (5.3)	1054 (13.4)	1034 (14.0)	20 (3.8)	1054 (13.4)
2006-2007	1176 (18.1)	252 (17.9)	1428 (18.1)	1348 (18.3)	80 (15.3)	1428 (18.1)
2008-2009	1337 (20.6)	418 (29.6)	1755 (22.2)	1597 (21.7)	158 (30.2)	1755 (22.2)
2010-2011	1328 (20.5)	386 (27.3)	1714 (21.7)	1560 (21.2)	154 (29.5)	1714 (21.7)
2012-2014	1663 (25.7)	282 (20.0)	1945 (24.6)	1833 (24.9)	112 (21.4)	1945 (24.6)
Year of birth						
Before 2000	2450 (37.8)	0 (0.0)	2450 (31.0)	2450 (33.2)	0 (0.0)	2450 (31.0)
2000-2003	2553 (39.4)	699 (49.5)	3252 (41.2)	3015 (40.9)	237 (45.2)	3252 (41.2)
2004-2005	685 (10.6)	442 (31.3)	1127 (14.3)	958 (13.0)	169 (32.3)	1127 (14.3)
2006-2007	479 (7.4)	180 (12.7)	659 (8.4)	591 (8.0)	68 (13.0)	659 (8.4)
2008-2009	248 (3.8)	81 (5.7)	329 (4.2)	283 (3.8)	46 (8.8)	329 (4.2)
2010 and beyond	68 (1.1)	11 (0.8)	79 (1.0)	75 (1.0)	4 (0.8)	79 (1.0)
WAZ- score (Mean (SD))	-1.48 (1.30)	-1.28 (1.26)	-1.43 (1.29)	-1.44 (1.31)	-1.37 (1.21)	-1.43 (1.29)
Age at ART start (years, median (IQR))	8.24 (5.89, 10.65)	5.16 (3.91, 6.73)	7.52 (5.25, 10.18)	7.81 (5.42, 10.33)	5.08 (4.0, 6.63)	7.52 (5.25, 10.18)
Infant PMTCT regimen						
No PMTCT		1 (0.1)			1 (0.2)	
SDNVP		1329 (94.1)			479 (91.4)	
SDNVP+AZT		76 (5.4)			42 (8.0)	
NVP 6 weeks		7 (0.5)			2 (0.4)	
Maternal PMTCT regimen						
SDNVP		1285 (90.9)			474 (90.6)	
SDNVP + AZT		126 (8.9)			45 (8.6)	
AZT only		1 (0.1)			1 (0.0)	

*Assumed to be ≥3 years

Table 3: Association between PMTCT exposure and VL >1000 copies/ml between 6-18 months on ART adjusted for other patient characteristics and calendar year of ART start.

	No assumptions made for unknown PMTCT		Assumptions: Unknown receive PMTCT according to date of birth		Assumptions: Unknown did not receive PMTCT	
Patient characteristics at ART start	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**
PMTCT						
No	1		1		1	
Yes	1.15	0.80, 1.66	0.86	0.69, 1.08	1.25	0.87, 1.79
Unknown	0.73	0.61, 0.89				
Gender						
Male	1		1		1	
Female	0.82	0.70, 0.96	0.82	0.70, 0.97	0.82	0.70, 0.97
WHO Stage						
Stages 1&2	1		1		1	
Stages 3&4	1.04	0.87, 1.25	1.06	0.89, 1.26	1.04	0.87, 1.24
WHO-defined Immunosuppression						
No	1		1		1	
Yes	3.15	2.60, 3.81	3.12	2.58, 3.77	3.11	2.57, 3.76
Calendar Year of ART start						
2004-2005	1		1		1	
2006-2007	0.83	0.59, 1.18	0.83	0.58, 1.17	0.80	0.57, 1.14
2008-2009	1.11	0.77, 1.60	1.13	0.79, 1.64	1.09	0.75, 1.56
2010-2011	1.20	0.78, 1.83	1.26	0.82, 1.93	1.19	0.78, 1.83
2012-2014	1.04	0.61, 1.77	1.13	0.67, 1.93	1.09	0.64, 1.85
Year of birth						
Before 2000	1		1		1	
2000-2003	1.24	0.91, 1.70	1.28	0.94, 1.76	1.27	0.92, 1.74
2004-2005	1.43	0.87, 2.35	1.50	0.91, 2.46	1.46	0.89, 2.40
2006-2007	2.02	1.09, 3.75	2.08	1.12, 3.84	2.11	1.14, 3.90
2008-2009	2.24	1.04, 4.83	2.27	1.06, 4.86	2.37	1.10, 5.09
2010 and beyond	1.74	0.60, 5.23	1.72	0.57, 5.18	1.89	0.63, 5.70
Age at ART start in years	1.08	1.02, 1.15	1.07	1.01 1.14	1.08	1.02 1.15

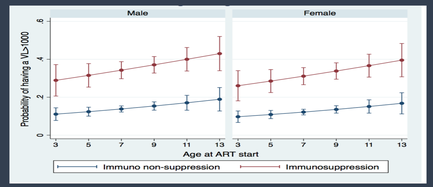

Figure 1: Predictive margins for VL > 1000 copies/ml by gender and baseline Immunosuppression status at ART start

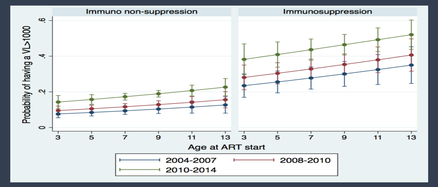

Figure 2: Predictive margins for VL > 1000 copies/ml and immunosuppression by calendar year of ART start

Conclusions

In this large cohort study, previous PMTCT exposure was not associated with poorer virologic outcomes in children >3 years starting EFV-based ART. However, immunosuppression at ART initiation was associated with virologic failure. Further research is needed to understand the effect of year of birth, correlated to PMTCT on VL outcomes.

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