

**Online only materials:**

**eTable 1: Frequency of Specific Major Congenital Anomalies within Anomaly Categories**

**eTable 2: Anomalies reported among children exposed to atazanavir during the first trimester**

**eTable 3: Association of Timing of First ARV Exposure During Pregnancy with Congenital Anomalies by ARV Drug Class and for Specific ARV Drugs**

**eTable 1. Frequency of Specific Major Congenital Anomalies within Anomaly Categories**

Anomaly Category	Total # of major anomalies (Total=242)	# of children with at least one anomaly in category (Total=201)	List of Major Anomalies
Musculoskeletal	72	59	Polydactyly (15), torticollis/muscular anomaly (12), clubfoot, talipes, other foot deformity (9), congenital dislocation of hip (5), craniosynostosis (4), plagiocephaly (4), pectus excavatum/funnel chest (3), lower limb anomaly (3), hypertelorism/other face or skull anomaly (3), spina bifida occulta/spine anomaly (3), syndactyly (3), inguinal hernia (2), diaphragmatic hernia/Morgagni, genu recurvatum/bowed legs, rib/sternum anomaly, scoliosis/congenital spine deformity, upper limb anomaly, upper limb reduction
Cardiovascular	55	41	Ventricular septal defect (13), patent foramen ovale (9), atrial septal defect (8), patent ductus arteriosus (7), pulmonary valve stenosis (5), atrioventricular canal (4), anomaly of coronary artery (2), pulmonary artery stenosis (2), bicuspid aortic valve, congenital mitral stenosis, hypoplastic left ventricle, tetralogy of Fallot, tricuspid valve regurgitation
Facial	20	17	Anomaly of eyelid/lacrimal system (5), branchial cleft (3), congenital cataract/lens anomaly (3), congenital hearing impairment (2), abnormal fascia, excess skin on neck, accessory auricle, agenesis of eye, corneal opacity, micrognathia, downward slanting eyes
Central Nervous System/Brain	19	14	Microcephaly (5), hydrocephaly (3), macrocephaly (3), spina bifida (2), tethered cord/spinal cord anomaly (2), anencephaly, anomaly of corpus callosum, encephalocele, holoprosencephaly
Male Genital	16	15	Hypospadias/chordee (8), cryptorchidism(7), congenital penile torsion
Renal	16	12	Congenital hydronephrosis (4), vesicoureteral reflux (4), renal agenesis or dysgenesis (2), renal cyst/polycystic kidney (2), accessory ureter, atresia/stenosis of urethra, ectopic kidney, obstructive defect of renal pelvis/ureter
Chromosomal	11	11	Trisomy 21 (Down Syndrome) (8), Trisomy 13 (Patau Syndrome), Mosaic Trisomy 8, duplication of chromosome
Skin	10	10	Hemangioma (4), lipoma (2), pigment disorder (2), cystic hygroma, teratoma
Mouth/Upper Gastrointestinal	7	7	Congenital pyloric stenosis (4), lip anomaly, macroglossia, malrotation of stomach
Cleft Disorders	4	3	Cleft lip and palate (3), cleft uvula
Respiratory	3	3	Anomaly of larynx/trachea (3)
Lower Gastrointestinal	3	3	Cystic/fibrocystic liver, Hirschsprung's disease, intestinal rotation
Other anomaly	6	5	Congenital adrenal hyperplasia (2), fetal alcohol syndrome, hemihypertrophy, situs inversus, Wolfe-Parkinson-White syndrome

**eTable 2. Anomalies reported among children exposed to atazanavir during the first trimester (also included in eTable 1)**

Anomaly Category	Total # of major anomalies (Total=39)	# of children with at least one anomaly in category (Total=33)	List of Major Anomalies
Musculoskeletal	13	11	Clubfoot/talipes/other foot deformity (2), polydactyly (2), torticollis (2), congenital dislocation of hip, craniosynostosis, rib/sternum anomaly, scoliosis/congenital spine deformity, spina bifida occulta, syndactyly, upper limb anomaly
Cardiovascular	9	7	Ventricular septal defect (4), anomaly of coronary artery, atrial septal defect, patent foramen ovale, pulmonary artery stenosis, pulmonary valve stenosis
Skin	3	3	Hemangioma (2), teratoma
Central Nervous System/Brain	3	2	Anomaly of corpus callosum, hydrocephaly, microcephaly
Renal	3	2	Congenital hydronephrosis (2), vesicoureteral reflux
Facial	2	2	Anomaly of eyelid/lacrimal system, congenital hearing impairment
Lower gastrointestinal	2	2	Cystic/fibrocystic liver, Hirschsprung's disease
Other types	4	4	<b>Chromosomal:</b> duplication of chromosome; <b>Male Genital:</b> hypospadias; <b>Mouth/Upper gastrointestinal:</b> congenital pyloric stenosis; <b>Other:</b> congenital adrenal hyperplasia

**eTable 3. Association of Timing of First ARV Exposure During Pregnancy with Congenital Anomalies by ARV Drug Class and for Specific ARV Drugs**

ARV Exposure	First exposure during pregnancy	% in category	Anomaly rate	Unadjusted Models		Adjusted Models*	
				OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Any ARV</b>	Never exposed	2.7	3/68 (4.4%)	1.00	ref	1.00	ref
	1st trimester	48.4	93/1219 (7.6%)	1.79 (0.55, 5.80)	0.33	2.34 (0.31, 17.40)	0.41
	2nd/3rd trimester	48.9	73/1230 (5.9%)	1.37 (0.42, 4.45)	0.60	1.97 (0.26, 14.68)	0.51
<b>HAART</b>	Never exposed	18.4	30/462 (6.5%)	1.00	ref	1.00	ref
	1st trimester	40.7	83/1025 (8.1%)	1.27 (0.83, 1.96)	0.28	1.14 (0.72, 1.82)	0.58
	2nd/3rd trimester	40.9	56/1029 (5.4%)	0.83 (0.53, 1.31)	0.43	0.79 (0.48, 1.28)	0.33
<b>PIs</b>	Never exposed	26.1	36/657 (5.5%)	1.00	ref	1.00	Ref
	1st trimester	35.2	75/887 (8.5%)	1.59 (1.06, 2.40)	0.026	1.39 (0.90, 2.16)	0.14
	2nd/3rd trimester	38.7	58/973 (6.0%)	1.09 (0.71, 1.68)	0.68	1.01 (0.64, 1.59)	0.98
<b>NNRTIs</b>	Never exposed	85.7	155/2156 (7.2%)	1.00	ref	1.00	ref
	1st trimester	8.5	13/214 (6.1%)	0.83 (0.47, 1.50)	0.55	0.91 (0.51, 1.65)	0.76
	2nd/3rd trimester	5.8	1/147 (0.7%)	0.09 (0.01, 0.64)	0.016	0.11 (0.02, 0.81)	0.030
<b>Among Specific ARV drugs**</b>							
<b>Abacavir (ABC)</b>	Never exposed	79.5	123/2002 (6.1%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	8.8	15/222 (6.8%)	1.11 (0.64, 1.93)	0.72	1.03 (0.58, 1.84)	0.91
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	11.6	31/293 (10.6%)	1.81 (1.19, 2.74)	0.005	1.75 (1.14, 2.68)	0.010
<b>Atazanavir (ATV)</b>	Never exposed	85.1	131/2143 (6.1%)	1.00	ref	1.00	Ref
	1st trimester	8.8	26/222 (11.7%)	2.04 (1.30, 3.18)	0.002	1.99 (1.26, 3.13)	0.003
	2nd/3rd trimester	6.0	12/152 (7.9%)	1.32 (0.71, 2.44)	0.38	1.28 (0.69, 2.38)	0.44
<b>Lamivudine (3TC)</b>	Never exposed	25.7	32/647 (4.9%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	31.7	63/797 (7.9%)	1.65 (1.06, 2.56)	0.025	1.41 (0.89, 2.24)	0.14
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	42.6	74/1073 (6.9%)	1.42 (0.93, 2.18)	0.105	1.37 (0.89, 2.13)	0.16
<b>Lopinavir (LPV/r)</b>	Never exposed	67.3	103/1693 (6.1%)	1.00	ref	1.00	Ref

ARV Exposure	First exposure during pregnancy	% in category	Anomaly rate	Unadjusted Models		Adjusted Models*	
				OR (95% CI)	P-value	OR (95% CI)	P-value
	1st trimester	13.5	32/341 (9.4%)	1.60 (1.06, 2.42)	0.027	1.40 (0.91, 2.17)	0.13
	2nd/3rd trimester	19.2	34/483 (7.0%)	1.17 (0.78, 1.75)	0.45	1.08 (0.71, 1.64)	0.73
<b>Nevirapine (NVP)</b>	Never exposed	90.9	161/2287 (7.0%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	4.6	7/115 (6.1%)	0.86 (0.39, 1.87)	0.70	0.99 (0.45, 2.18)	0.98
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	4.6	1/115 (0.9%)	0.12 (0.02, 0.83)	0.032	0.16 (0.02, 1.15)	0.069
<b>Ritonavir (as booster)</b>	Never exposed	47.1	70/1186 (5.9%)	1.00	ref	1.00	Ref
	1st trimester	25.2	59/635 (9.3%)	1.63 (1.14, 2.34)	0.008	1.49 (1.02, 2.19)	0.042
	2nd/3rd trimester	27.7	40/696 (5.7%)	0.97 (0.65, 1.45)	0.89	0.90 (0.59, 1.38)	0.63
<b>Stavudine (d4T)</b>	Never exposed	95.9	159/2414 (6.6%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	2.7	4/68 (5.9%)	0.89 (0.32, 2.47)	0.82	1.15 (0.41, 3.23)	0.79
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	1.4	6/35 (17.1%)	2.93 (1.20, 7.17)	0.018	3.23 (1.21, 8.63)	0.019
<b>Zidovudine (ZDV)</b>	Never exposed	24.9	31/627 (4.9%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	28.8	57/726 (7.9%)	1.64 (1.04, 2.57)	0.032	1.44 (0.90, 2.32)	0.13
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	46.2	81/1164 (7.0%)	1.44 (0.94, 2.20)	0.095	1.47 (0.95, 2.29)	0.083
<b>Among Selected Combinations</b>							
<b>Zidovudine plus Lamivudine</b>	Never exposed	30.3	35/763 (4.6%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	27.2	57/684 (8.3%)	1.89 (1.22, 2.92)	0.004	1.58 (1.00, 2.50)	0.048
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	42.5	77/1070 (7.2%)	1.61 (1.07, 2.43)	0.023	1.56 (1.02, 2.38)	0.039
<b>Didanosine plus Stavudine</b>	Never exposed	99.5	166/2505 (6.6%)	1.00	ref	1.00	Ref
	1 <sup>st</sup> trimester	0.3	2/7 (28.6%)	5.64 (1.09, 29.27)	0.040	8.17 (1.52, 43.8)	0.014
	2 <sup>nd</sup> /3 <sup>rd</sup> trimester	0.2	1/5 (20.0%)	3.53 (0.39, 31.72)	0.26	NE	---

OR=odds ratio, CI=confidence interval, NE=not estimated due to sparse data, HAART=highly active antiretroviral treatment, PI=protease inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor

\*Adjusted model includes birth cohort and low early CD4 (<250 cells/uL); \*\* Specific ARV drugs and ARV combinations were included if they had a significant or marginally significant association with congenital anomaly case status for at least one time period (either 1<sup>st</sup> trimester or 2<sup>nd</sup>/3<sup>rd</sup> trimester, as compared to never exposed).