CONFIDENTIAL

Pediatric HIV/AIDS Cohort Study (PHACS)
Surveillance Monitoring of ART Toxicities (SMARTT) Study
Annual Administrative Report

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Use: This report is intended primarily for generating data analysis concept sheets and substudy proposals for PHACS. Information contained in the report also may be used in presentations and published manuscripts with acknowledgement or citation.

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Tables:

Figures:

Summary

As of April 1, 2017, 4088 children and 3136 caregivers enrolled in SMARTT (**Table 1**). As shown in the table, there were 2609 children in the dynamic cohort and 1240 in the static cohort (enrollment for the static cohort was closed on July 31, 2009). Starting in March 2010, a cohort of 200 HIV-unexposed, uninfected children was enrolled (50 each from four specific age groups [1, 3, 5, and 9 years old]) to serve as a reference group. After enrollment into the reference cohort began, echocardiograms were added to the schedule of evaluations for 3- and 5-year olds. In order to ensure a sufficient number of echocardiograms, 35 additional children from the 3- and 5-year old groups were enrolled into a modified reference cohort. A total of 239 children were enrolled in the reference cohort and evaluations are now complete. These children completed a limited set of evaluations including echocardiograms.

Enrollment by site is summarized in **Table 2**. For the static cohort, most children (79%) previously participated in a PACTG/IMPAACT protocol: 24% in P1025 only; 23% in 219/219C; 13% in WITS only; 7% in 219/219C and WITS; 6% in 219C and P1025; 2% in 219C, P1025 and WITS (**Table 3**). Approximately half of the children enrolled were male (**Table 4**). Most children were Black or African American (65%), and 29% were of Hispanic ethnicity. The median age at enrollment of children in the static cohort was 4.1 years. The numbers of children enrolled in the different age groups of the reference cohort are: 52 one-year olds; 67 three-year olds; 71 five-year olds and 49 nine-year olds.

As shown in **Table 5**, 79% of infants were born at at least 37 weeks gestation and the majority weighed at least 2500 g (83%). The mode of delivery was known in 99% of children with some delivery information obtained, with 44% delivered by spontaneous vaginal delivery, 40% delivered by C-section before labor/membrane rupture and 13% delivered by C-section after labor/membrane rupture. [Note that the dynamic cohort allows study entry during gestation; thus birth characteristics may not yet be available]. Of the children enrolled in the dynamic and static cohorts, 85% and 71% children are still on study as of the last data retrieval date, respectively; 293 (11%) dynamic and 199 (16%) static children were withdrawn / lost to follow-up; and 56 (2%) dynamic and 52 (4%) static children were off study because of site closure (**Table 6**). A total of 31 children were off study because of death: 12 cases of intrauterine fetal demise, 4 of SIDS, 2 of complication from extensive burn, 1 of acute lymphoblastic leukemia, 1 of complication of Trisomy 21, 1 of motor vehicle accident, 1 of extreme prematurity, 1 of septic shock, 1 secondary to gunshot wound, 1 cardiac arrest, 1 chromosomal microdeletion syndrome, and 5 undetermined. Nine dynamic children have gone off study due to HIV infection. Among children in the dynamic and static cohorts who were still on study, the median age at the last clinic visit for the dynamic and static cohorts were 4 and 11 years, respectively (**Table 7**). Overall, 97% of the children enrolled completed the entry visit and 89% of visits were done on time or early (**Table 8**). Four children missed the entry visit and 87 (2%) children dropped out of the study before the first study visit.

Tables 9 - 14 contain some initial summaries of key measures across domains of interest for SMARTT, including cognitive assessments (Tables 9 and 10), hearing and language assessments (Tables 11 and 12), growth data (Table 13), and maternal substance use during pregnancy (Table 14).

Table 9 summarizes the results of the Bayley Screen for three-year olds. Of the participants assessed, 33-56% of the dynamic cohort, 31-53% of the static cohort and 16-49% of the reference cohort were at risk (at risk/some risk) of developmental delay across the different sub-domains, with the highest percentage for cognitive delay and lowest percentage for gross motor delay. Overall, at least 45 participants were identified to require further evaluation for delay in at least one of the assessed skills categories.

Neurodevelopment assessments for other ages are summarized in **Table 10**, including the Full Bayley-III (1-year olds), WPPSI (5-year olds), WASI and WIAT for 7 years and older (performed at age-specific visits according to protocol), and BRIEF-SR for those 11 years and older (performed at age-specific visits according to protocol). The normative scores for the Bayley -III, WPPSI, WASI and WIAT have a mean of 100 and a standard deviation of 15. The normative scores for the BRIEF have a mean of 50 and a standard deviation of 10. As shown in the table, the mean scores across different neurodevelopment batteries were mostly within 5 – 10 points of the general population norms.

Information related to caregiver-reported hearing information is summarized in **Table 11**, which indicates that overall, 26% of children (24% of dynamic cohort, 29% of static cohort and 21% of reference cohort) had an audiologic exam before enrolling in the study; 7 (all from the static cohort) of whom were identified with permanent hearing loss. Summary measures for the age-specific language assessments are provided in **Table 12**, including the MacArthur CDI (1-year olds), Ages and Stages Questionnaire (ASQ: 2-year olds), TELD (3-year olds), and TOLD (5-year olds). The normative scores are 50th percentile for the CDI, and 100 (standard deviation: 15) for TELD and TOLD. The general population means are age specific for the ASQ. As shown in the table, the mean scores of MacArthur CDI, TELD and TOLD were mostly within 5 – 10 points of the general population; the means of ASQ were about 45.

The growth measurements in **Table 13** suggest that infants enrolled in the dynamic cohort were below average length and weight at birth, while those in the static cohort and reference cohort were above average height/length and weight for their ages at the time of study entry. The mean BMI (≥ 2 years old) for the static cohort and reference cohort were also higher than average.

Table 14 summarizes self-reported substance use during pregnancy by mothers in the dynamic cohort, by trimester of pregnancy. Overall, 599 (30%) women reported some substance use (licit or illicit) at some point during their pregnancy. Substance use was highest during the first trimester and then decreased; cigarette smoking (18%) was the most frequently reported substance, followed by alcohol (10%) and marijuana (9%).

In utero ARV exposure by birth year for static and dynamic cohorts combined is summarized in **Table 15**. Overall, of the 3688 children who completed a scheduled study visit, 3526 (96%) were exposed *in utero* to an ARV; 45 (1%) were exposed to ARV during labor and delivery only; while 38 (1%) were not exposed to any ARV during pregnancy, labor, or delivery.

Figure 1 - Figure 4 show the trends of *in utero* ARV exposure by year of birth, for each ARV class and the individual agents within each class. Calculations are based on the number of children with *in utero* ARV exposure data available. Prenatal exposure to NRTI-containing regimens remained very high (nearly 100%) across all birth years (**Figure 1**). There was a decreasing trend in zidovudine (ZDV) exposure over time (from 100% in 1995 to about 21% in 2016); lamivudine (3TC) exposure increased dramatically from about 5% in 1996 to more than 90% in 2000 and fluctuated around this percentage till 2005, then decreased thereafter with a similar trend as ZDV; abacavir (ABC) became a common NRTI agent received during pregnancy after 2002, with use decreasing after 2007; tenofovir (TDF) and emtricitabine (FTC) use increased consistently from about 3% in 2002 to about 77% in 2016, and from about 1% in 2004 to about 77% in 2016, respectively; in addition, TDF and FTC surpassed ZDV and 3TC as the most commonly used NRTI agents in 2012. The use of NNRTI-containing regimens increased from about 5% in 1996 to more than 30% in 2003, then decreased to about 10% between 2008 and 2011 and then increased again to about 34% in 2015 (**Figure 2**). Nevirapine (NPV) was the most commonly used NNRTI agent, with use increasing between 1996 and 2003, and decreasing since then (less than 1% exposure in 2016); the use of efavirenz (EFV) was consistently low (less than 10%); there has been an increasing trend in the use of rilpivirine (RPV) since 2012 (increased from 4% in 2012 to about 30% in 2015). Starting in 1997, the use of PI-containing regimens increased to about 86% in 2010, and decreased since then (**Figure 3**). Nelfinavir (NFV) was initially the most commonly-used PI, but in 2007 it was surpassed by use of ritonavir boosted PIs, and that trend continues. Lopinavir/r exposure increased between 2001 and 2009 and has decreased since then. There was also an increasing trend in the use of atazanavir between 2004 and 2013; use has decreased since then. The first reported use of a Fusion Inhibitor (FI) was in 2006 and of an Integrase Inhibitor (II) was in 2008 (**Figure 4**); use of the FIs enfurvirtide (ENF) and maraviroc (MVC) have remained low; use of the II raltegravir (RAL) increased from about 1% in 2008 to about 15% in 2013, and then decreased to about 7% in 2016; use of elvitegravir (EVG) paired with cobicistat (a non-ARV booster for EVG), and in combination with FTC and TDF (as Stribild) emerged in 2013 and increased from 1% to about 15% in 2016; dolutegravir (DTG) use was first reported in 2014 at about 2% and increased to about 19% in 2016. The most commonly-used regimen has changed over time; ZDV monotherapy was the most commonly-used regimen before 1999, then ZDV+3TC in 1999, ZDV+3TC+NFV between 2000 and 2007, and ZDV+3TC+lopinavir/r after 2007 until 2014 when TDF+FTC+boosted ATV became the most frequently used regimen in 2014 and TDF+FTC+RPV after 2014 (**Figure 5**).

The median duration of follow-up in SMARTT was 103 months among Static and 51 months among Dynamic participants. The follow-up time is based on the assumption that a participant is still on study as of the last data retrieval date unless known to have discontinued. It is not based on their last study visit.

Tables and Figures

Table 1: SMARTT - Study Enrollment by Cohort and Quarter

		Cohort			
		Caregiver (N=3136)	Dynamic (N=2609)	Static (N=1240)	Reference (N=239)
Enrollment quarter	2007 Q1	4 (0%)	0 (0%)	5 (0%)	0 (0%)
	2007 Q2	167 (5%)	28 (1%)	185 (15%)	0 (0%)
	2007 Q3	204 (7%)	51 (2%)	227 (18%)	0 (0%)
	2007 Q4	145 (5%)	51 (2%)	127 (10%)	0 (0%)
	2008 Q1	183 (6%)	79 (3%)	149 (12%)	0 (0%)
	2008 Q2	142 (5%)	77 (3%)	95 (8%)	0 (0%)
	2008 Q3	130 (4%)	79 (3%)	84 (7%)	0 (0%)
	2008 Q4	126 (4%)	80 (3%)	106 (9%)	0 (0%)
	2009 Q1	127 (4%)	89 (3%)	90 (7%)	0 (0%)
	2009 Q2	128 (4%)	79 (3%)	109 (9%)	0 (0%)
	2009 Q3	113 (4%)	81 (3%)	63 (5%)	0 (0%)
	2009 Q4	65 (2%)	78 (3%)	0 (0%)	0 (0%)
	2010 Q1	56 (2%)	61 (2%)	0 (0%)	2 (1%)
	2010 Q2	73 (2%)	73 (3%)	0 (0%)	8 (3%)
	2010 Q3	82 (3%)	72 (3%)	0 (0%)	30 (13%)
	2010 Q4	82 (3%)	61 (2%)	0 (0%)	38 (16%)
	2011 Q1	90 (3%)	74 (3%)	0 (0%)	41 (17%)
	2011 Q2	67 (2%)	63 (2%)	0 (0%)	25 (10%)
	2011 Q3	83 (3%)	61 (2%)	0 (0%)	52 (22%)
	2011 Q4	58 (2%)	65 (2%)	0 (0%)	5 (2%)
	2012 Q1	56 (2%)	57 (2%)	0 (0%)	10 (4%)
	2012 Q2	66 (2%)	74 (3%)	0 (0%)	12 (5%)
	2012 Q3	49 (2%)	56 (2%)	0 (0%)	7 (3%)
	2012 Q4	43 (1%)	49 (2%)	0 (0%)	6 (3%)
	2013 Q1	50 (2%)	64 (2%)	0 (0%)	3 (1%)
	2013 Q2	58 (2%)	73 (3%)	0 (0%)	0 (0%)
	2013 Q3	61 (2%)	75 (3%)	0 (0%)	0 (0%)
	2013 Q4	53 (2%)	67 (3%)	0 (0%)	0 (0%)
	2014 Q1	54 (2%)	65 (2%)	0 (0%)	0 (0%)
	2014 Q2	47 (1%)	61 (2%)	0 (0%)	0 (0%)
	2014 Q3	43 (1%)	58 (2%)	0 (0%)	0 (0%)
	2014 Q4	43 (1%)	60 (2%)	0 (0%)	0 (0%)
	2015 Q1	51 (2%)	64 (2%)	0 (0%)	0 (0%)
	2015 Q2	46 (1%)	62 (2%)	0 (0%)	0 (0%)
	2015 Q3	52 (2%)	68 (3%)	0 (0%)	0 (0%)
	2015 Q4	44 (1%)	77 (3%)	0 (0%)	0 (0%)

	Cohort			
	Caregiver (N=3136)	Dynamic (N=2609)	Static (N=1240)	Reference (N=239)
2016 Q1	40 (1%)	56 (2%)	0 (0%)	0 (0%)
2016 Q2	38 (1%)	51 (2%)	0 (0%)	0 (0%)
2016 Q3	42 (1%)	57 (2%)	0 (0%)	0 (0%)
2016 Q4	33 (1%)	46 (2%)	0 (0%)	0 (0%)
2017 Q1	42 (1%)	67 (3%)	0 (0%)	0 (0%)

Reference cohort started enrolling in Q1 of 2010

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Table 2: SMARTT - Study Enrollment by Site

			Cohort		
		Total (N=4088)	Dynamic (N=2609)	Static (N=1240)	Reference (N=239)
Enrollment site	NYU MEDICAL CTR/BELLEVUE	129 (3%)	71 (3%)	58 (5%)	0 (0%)
	UNIVERSITY OF ALABAMA AT BIRMINGHAM *	181 (4%)	128 (5%)	29 (2%)	24 (10%)
	UNIVERSITY OF SOUTHERN CALIFORNIA	351 (9%)	267 (10%)	84 (7%)	0 (0%)
	SAN JUAN RESEARCH HOSPITAL	134 (3%)	73 (3%)	61 (5%)	0 (0%)
	ST. JUDE CHILDREN'S RESEARCH HOSPITAL *	297 (7%)	229 (9%)	44 (4%)	24 (10%)
	SUNY DOWNSTATE MEDICAL CENTER *	257 (6%)	116 (4%)	119 (10%)	22 (9%)
	UNIV OF COLORADO HEALTH SCIENCES CENTER	209 (5%)	145 (6%)	64 (5%)	0 (0%)
	NEW JERSEY MEDICAL CENTER	99 (2%)	91 (3%)	8 (1%)	0 (0%)
	SUNY STONY BROOK MEDICAL CENTER	25 (1%)	8 (0%)	17 (1%)	0 (0%)
	CHILDREN'S DIAG AND TREAT CTR (S FLOR) *	139 (3%)	91 (3%)	22 (2%)	26 (11%)
	BRONX/LEBANON HOSPITAL CENTER *	441 (11%)	263 (10%)	137 (11%)	41 (17%)
	UNIVERSITY OF FLORIDA HEALTH SCIENCE CTR	276 (7%)	178 (7%)	98 (8%)	0 (0%)
	UNIVERSITY OF ILLINOIS (CHICAGO) *	217 (5%)	108 (4%)	88 (7%)	21 (9%)
	UNIVERSITY OF PUERTO RICO MEDICAL CENTER	208 (5%)	118 (5%)	90 (7%)	0 (0%)
	CHILDREN'S HOSPITAL OF PHILADELPHIA	27 (1%)	20 (1%)	7 (1%)	0 (0%)
	UNIVERSITY OF MIAMI *	357 (9%)	278 (11%)	40 (3%)	39 (16%)
	TEXAS CHILDREN'S HOSPITAL (BAYLOR) *	241 (6%)	135 (5%)	82 (7%)	24 (10%)
	UNIVERSITY HEALTH SCIENCE CTR (TULANE) *	113 (3%)	84 (3%)	11 (1%)	18 (8%)
	UCSD MEDICAL CENTER	109 (3%)	71 (3%)	38 (3%)	0 (0%)
	UNIVERSITY OF MARYLAND MED CTR	42 (1%)	24 (1%)	18 (1%)	0 (0%)
	JACOBI MEDICAL CENTER	35 (1%)	12 (0%)	23 (2%)	0 (0%)
	CHILDREN'S MEMORIAL HOSPITAL OF CHICAGO	201 (5%)	99 (4%)	102 (8%)	0 (0%)

*Sites with * enroll reference cohort*

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Table 3: SMARTT - Enrollment by Previous Protocol Participation (Static cohort only)

Protocol group	Studies	Static (N=1240)
No Previous Protocol	None	264 (21%)
219/219C/P1025	P1025+NATURAL HISTORY	1 (0%)
	P1025	293 (24%)
	219C+P1025	75 (6%)
	219/219C	291 (23%)
	219	2 (0%)
	Total	662 (53%)
WITS Only	WITS	159 (13%)
219/219C/P1025+WITS	P1025+WITS	5 (0%)
	219C+P1025+WITS	20 (2%)
	219/219C+WITS	90 (7%)
	Total	115 (9%)
Other PACTG/IMPAACT	PACTG 1039	3 (0%)
	PACTG 1025	1 (0%)
	PACTG 1022	1 (0%)
	ACTG A5084	2 (0%)
	ACTG 394	1 (0%)
	ACTG 367	1 (0%)
	ACTG 354	1 (0%)
	ACTG 353	2 (0%)
	ACTG 326	2 (0%)
	ACTG 316/247	1 (0%)
	ACTG 316	7 (1%)
	ACTG 247	1 (0%)
	Total	23 (2%)
Other	PACTG 386	1 (0%)
	NATURAL HISTORY	15 (1%)
	CHS	1 (0%)
	Total	17 (1%)

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Above table summarizes enrollment in previous studies based on the information provided at PHACS enrollment. 219/219C, P1025, and WITS enrollment information was captured for all static participants. However, enrollment information for other studies was only captured at PHACS enrollment for participants who did not participate in 219/219C, P1025, or WITS. Children in the dynamic cohort may also be enrolled in other studies (e.g. P1025).

Table 4: SMARTT - Enrollment Demographics

			Cohort		
		Total (N=4088)	Dynamic (N=2609)	Static (N=1240)	Reference (N=239)
Sex	Male	2070 (51%)	1308 (50%)	643 (52%)	119 (50%)
	Female	1941 (47%)	1224 (47%)	597 (48%)	120 (50%)
	Missing - Form not submitted	77 (2%)	77 (3%)	0 (0%)	0 (0%)
Age* at enrollment (yrs)	Median	4.1	.	4.1	4.7
	Birth	2638 (65%)	2609 (100%)	29 (2%)	0 (0%)
	1-2	404 (10%)	0 (0%)	352 (28%)	52 (22%)
	3-4	358 (9%)	0 (0%)	291 (23%)	67 (28%)
	5-6	277 (7%)	0 (0%)	206 (17%)	71 (30%)
	7-12	411 (10%)	0 (0%)	362 (29%)	49 (21%)
Race	Asian	20 (0%)	9 (0%)	7 (1%)	4 (2%)
	Native Hawaiian or other Pacific Islander	3 (0%)	2 (0%)	1 (0%)	0 (0%)
	Black or African American	2676 (65%)	1741 (67%)	765 (62%)	170 (71%)
	White	1054 (26%)	645 (25%)	350 (28%)	59 (25%)
	American Indian	7 (0%)	6 (0%)	1 (0%)	0 (0%)
	More than One Race	123 (3%)	100 (4%)	23 (2%)	0 (0%)
	Participant does not want to report	8 (0%)	3 (0%)	4 (0%)	1 (0%)
	Participant does not know	77 (2%)	41 (2%)	32 (3%)	4 (2%)
	Race not available to clinic	120 (3%)	62 (2%)	57 (5%)	1 (0%)
Ethnicity	Hispanic or Latino	1201 (29%)	723 (28%)	424 (34%)	54 (23%)
	Not Hispanic or Latino	2839 (69%)	1850 (71%)	806 (65%)	183 (77%)
	More than one ethnicity	42 (1%)	34 (1%)	8 (1%)	0 (0%)
	Participant does not want to report	1 (0%)	0 (0%)	1 (0%)	0 (0%)
	Participant does not know	4 (0%)	2 (0%)	1 (0%)	1 (0%)
	Ethnicity not available to clinic	1 (0%)	0 (0%)	0 (0%)	1 (0%)

**Age is rounded to the nearest year. So a child who enrolled at 4 years 11 months is in the 5-6 year group.*

Age at enrollment for reference cohort is 1, 3, 5 or 9 years old

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Table 5: SMARTT - Baseline Maternal Pregnancy and Delivery History Characteristics

Characteristic		Total (N=3902)	Cohort Dynamic (N=2496)	Static (N=1178)	Reference (N=228)
Gestational Age at Birth*	<32	90 (2%)	54 (2%)	31 (3%)	5 (2%)
	32-<37	630 (16%)	400 (16%)	205 (17%)	25 (11%)
	>=37	3,071 (79%)	2,031 (81%)	860 (73%)	180 (79%)
	Unknown	111 (3%)	11 (0%)	82 (7%)	18 (8%)
Weight at Birth	<2500 g	671 (17%)	415 (17%)	219 (19%)	37 (16%)
	>=2500 g	3,230 (83%)	2,080 (83%)	959 (81%)	191 (84%)
	Unknown	1 (0%)	1 (0%)	0 (0%)	0 (0%)
Mode of Delivery	Spontaneous Vaginal	1,726 (44%)	1,022 (41%)	556 (47%)	148 (65%)
	Assisted Vaginal (Forceps, Vacuum)	70 (2%)	30 (1%)	25 (2%)	15 (7%)
	C-Section Before Labor/Membrane Rupture	1,571 (40%)	1,085 (43%)	449 (38%)	37 (16%)
	C-Section After Labor/Membrane Rupture	514 (13%)	354 (14%)	132 (11%)	28 (12%)
	Unknown Delivery Mode	21 (1%)	5 (0%)	16 (1%)	0 (0%)
Apgar Score at One Minute	< 7	345 (9%)	253 (10%)	92 (8%)	0 (0%)
	>=7	3,166 (81%)	2,211 (89%)	955 (81%)	0 (0%)
	Unknown	391 (10%)	32 (1%)	131 (11%)	228 (100%)
Apgar Score at Minute Five	< 7	69 (2%)	52 (2%)	17 (1%)	0 (0%)
	>=7	3,445 (88%)	2,414 (97%)	1,031 (88%)	0 (0%)
	Unknown	388 (10%)	30 (1%)	130 (11%)	228 (100%)

Above calculations are based on 4088 children enrolled in the study: 1240 in the static cohort, 2609 in the dynamic cohort and 239 in the reference cohort. In the static cohort, 41 children did not have forms submitted at this time and 21 did not have their submitted forms completed. In the dynamic cohort, 94 children did not have forms submitted at this time and 19 did not have their submitted forms completed. In the reference cohort, 3 children did not have forms submitted at this time and 8 did not have their submitted forms completed.

** Gestational age is first based on obstetrical gestational age data and when not available, then pediatric gestational age.*

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Table 6: SMARTT - Study Status

			Cohort		
		Total (N=4088)	Dynamic (N=2609)	Static (N=1240)	Reference (N=239)
Study status	Still on study	3092 (76%)	2215 (85%)	877 (71%)	0 (0%)
	Completed study	337 (8%)	0 (0%)	106 (9%)	231 (97%)
	Enrollment error / eligibility failure*	11 (0%)	9 (0%)	2 (0%)	0 (0%)
	Death of participant/parent/guardian	31 (1%)	29 (1%)	2 (0%)	0 (0%)
	Withdrawal / loss to follow-up	499 (12%)	293 (11%)	199 (16%)	7 (3%)
	Site closure	108 (3%)	56 (2%)	52 (4%)	0 (0%)
	Other reason	10 (0%)	7 (0%)	2 (0%)	1 (0%)

** 9 Dynamic children in the Enrollment error/eligibility failure category are HIV-infected*

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Table 7: SMARTT - Age at Last Scheduled Clinic Visit Among Participants Still on Study

			Cohort	
Characteristic		Total (N=3092)	Dynamic (N=2215)	Static (N=877)
Age at Last Scheduled Clinical Visit	Median (Min, Max)	5.2 (0.0, 21.1)	4.0 (0.0, 9.6)	11.1 (6.7, 21.1)
	0	287 (9%)	287 (13%)	0 (0%)
	1-2	479 (15%)	479 (22%)	0 (0%)
	3-4	473 (15%)	473 (21%)	0 (0%)
	5-6	452 (15%)	452 (20%)	0 (0%)
	7-12	1,141 (37%)	524 (24%)	617 (70%)
	13-15	219 (7%)	0 (0%)	219 (25%)
	>15	41 (1%)	0 (0%)	41 (5%)

** For participants who did not attend the scheduled study visits, the scheduled clinical visit date was used to calculate the age.*

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Table 8: SMARTT - Entry Visit Status

Visit status	Total	Cohort		
		Dynamic	Static	Reference
Visit reported	**3960 (97%)**	**2524 (97%)**	**1200 (97%)**	**236 (99%)**
Early	26 (1%)	1 (0%)	21 (2%)	4 (2%)
In window	3579 (88%)	2377 (91%)	999 (81%)	203 (85%)
Late	355 (9%)	146 (6%)	180 (15%)	29 (12%)
No visit reported	**128 (3%)**	**85 (3%)**	**40 (3%)**	**3 (1%)**
Delinquent	1 (0%)	1 (0%)	0 (0%)	0 (0%)
In window	36 (1%)	36 (1%)	0 (0%)	0 (0%)
Missed visit	4 (0%)	4 (0%)	0 (0%)	0 (0%)
Off study	87 (2%)	44 (2%)	40 (3%)	3 (1%)

Table (above) reports on the status and timeliness of the entry visit for all enrolled participants. This is based on the Visit Report form (PH5801) and the participant's birthday. For the static cohort and reference cohort, the allowed visit window is the birthday +/- 90 days.

For the dynamic cohort, the permitted visit window is from after birth up to two weeks. A visit is Delinquent if no visit has been reported, the visit window has passed, and an additional 2 weeks have passed (to allow time for submission of PH5801). This is a total of 4 weeks from an infant's birthdate. For those infants with no recorded birthdate, an estimated delivery date has been generated based on 43 weeks of gestation (or the visit date on PH5801).

Table 9: Bayley Screen for Three Year-Olds

ND Assessment		Total (N=1228)	Cohort: Dynamic (N=910)	Cohort: Static (N=275)	Cohort: Reference (N=43)
Cognitive	At Risk for Devl Delay/Further Eval Needed	45 (3.7%)	34 (3.7%)	11 (4.0%)	0 (0.0%)
	Some Risk for Devl Delay	636 (51.8%)	480 (52.7%)	135 (49.1%)	21 (48.8%)
	Low Risk for Devl Delay	547 (44.5%)	396 (43.5%)	129 (46.9%)	22 (51.2%)
Receptive Communication	At Risk for Devl Delay/Further Eval Needed	28 (2.3%)	17 (1.9%)	11 (4.0%)	0 (0.0%)
	Some Risk for Devl Delay	456 (37.1%)	345 (37.9%)	97 (35.3%)	14 (32.6%)
	Low Risk for Devl Delay	742 (60.4%)	546 (60.0%)	167 (60.7%)	29 (67.4%)
	Not Done	2 (0.2%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Expressive Communication	At Risk for Devl Delay/Further Eval Needed	43 (3.5%)	34 (3.7%)	9 (3.3%)	0 (0.0%)
	Some Risk for Devl Delay	499 (40.6%)	381 (41.9%)	108 (39.3%)	10 (23.3%)
	Low Risk for Devl Delay	683 (55.6%)	492 (54.1%)	158 (57.5%)	33 (76.7%)
	Not Done	3 (0.2%)	3 (0.3%)	0 (0.0%)	0 (0.0%)
Fine Motor	At Risk for Devl Delay/Further Eval Needed	29 (2.4%)	21 (2.3%)	8 (2.9%)	0 (0.0%)
	Some Risk for Devl Delay	465 (37.9%)	362 (39.8%)	91 (33.1%)	12 (27.9%)
	Low Risk for Devl Delay	732 (59.6%)	525 (57.7%)	176 (64.0%)	31 (72.1%)
	Not Done	2 (0.2%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Gross Motor	At Risk for Devl Delay/Further Eval Needed	22 (1.8%)	16 (1.8%)	6 (2.2%)	0 (0.0%)
	Some Risk for Devl Delay	370 (30.1%)	285 (31.3%)	78 (28.4%)	7 (16.3%)
	Low Risk for Devl Delay	833 (67.8%)	606 (66.6%)	191 (69.5%)	36 (83.7%)
	Not Done	3 (0.2%)	3 (0.3%)	0 (0.0%)	0 (0.0%)

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Table 10: Age-specific ND Assessments

		Cohort					
		Dynamic		Static		Reference	
ND Assessment	Score	N	Mean (S.D)	N	Mean (S.D)	N	Mean (S.D)
Bayley-III (1 year old)	Cognitive, Composite	1332	103.2 (14.0)	146	102.9 (15.2)	49	102.2 (14.0)
	Language, Composite	1330	94.7 (13.6)	145	93.2 (14.7)	49	95.1 (12.5)
	Motor, Composite	1324	97.5 (12.7)	145	96.9 (15.9)	49	100.9 (14.7)
	Social-Emotional, Composite	1295	101.7 (17.4)	142	101.6 (18.5)	49	100.5 (16.4)
	General Adaptive, Composite	1292	94.9 (14.4)	142	93.4 (15.0)	49	92.3 (11.3)
WPPSI (5 years old)	Full Scale IQ	580	94.5 (15.1)	445	94.6 (14.5)	47	93.6 (15.6)
	Performance IQ	593	96.3 (15.3)	447	97.3 (15.2)	47	95.6 (15.3)
	Verbal IQ	591	92.3 (14.5)	447	92.1 (12.9)	47	91.6 (13.9)
	Processing Speed IQ	568	95.5 (15.7)	442	96.3 (15.9)	47	95.0 (15.4)
	General Language IQ	344	93.1 (13.6)	210	91.0 (14.1)	19	91.1 (11.4)
WASI (7+ odd years old)*	Full Scale IQ	53	99.3 (14.8)	759	97.8 (13.9)	48	100.8 (12.6)
	Performance IQ	53	96.1 (14.1)	759	95.1 (13.0)	49	95.3 (13.0)
	Verbal IQ	53	102.9 (18.4)	759	100.9 (15.8)	48	105.8 (14.2)
WIAT (7+ odd years old)*	Word Reading, Standard Score	53	99.6 (15.6)	758	97.3 (16.0)	49	97.1 (15.0)
	Spelling, Standard Score	53	99.3 (17.2)	755	97.9 (16.3)	48	98.8 (15.8)
	Numerical Operations, Standard Score	53	94.1 (17.1)	758	93.9 (16.5)	49	94.5 (15.5)
BRIEF (11+ odd years old)*	Inhibit, T-Score	0		136	48.6 (9.7)	0	
	Shift, T-Score	0		136	52.7 (12.2)	0	
	Emotional Control, T-Score	0		136	50.7 (10.2)	0	
	Monitor, T-Score	0		135	48.9 (10.5)	0	
	Behavioral Regulation Index, T-Score	0		135	50.4 (11.4)	0	
	Working Memory, T-Score	0		136	50.9 (11.3)	0	
	Plan/Organize, T-Score	0		136	47.3 (10.4)	0	
	Organization of Materials, T-Score	0		136	48.4 (9.9)	0	
	Task Completion, T-Score	0		134	49.6 (10.1)	0	
	Metacognition Index, T-Score	0		135	48.9 (10.9)	0	
	Global Executive Composite, T-Score	0		135	49.6 (11.3)	0	
	Behavioral Shift, T-Score	0		134	51.7 (11.8)	0	
	Cognitive Shift, T-Score	0		134	52.6 (11.3)	0	

** WASI, WIAT AND BRIEF: For participants completing an assessment at more than one time point, the earliest assessment is used.*

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Table 11: SMARTT Caregiver-Reported Hearing Information at Entry

Characteristic		Total (N=3950)	Cohort: Dynamic (N=2519)	Cohort: Static (N=1195)	Cohort: Reference (N=236)
Concerns about hearing?	Yes	123 (3%)	37 (1%)	77 (6%)	9 (4%)
	No	3,782 (96%)	2,445 (97%)	1,111 (93%)	226 (96%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Child has repeated ear infections?	Yes	124 (3%)	0 (0%)	102 (9%)	22 (9%)
	No	3,781 (96%)	2,482 (99%)	1,086 (91%)	213 (90%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Child failed hearing screening?	Yes	142 (4%)	66 (3%)	65 (5%)	11 (5%)
	No	3,763 (95%)	2,416 (96%)	1,123 (94%)	224 (95%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Child tested by audiologist?	Yes	1,013 (26%)	614 (24%)	349 (29%)	50 (21%)
	No	2,892 (73%)	1,868 (74%)	839 (70%)	185 (78%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Perm hearing loss in 1-2 ears?	Yes	7 (0%)	0 (0%)	7 (1%)	0 (0%)
	No	1,004 (25%)	612 (24%)	342 (29%)	50 (21%)
	Not Required	2,893 (73%)	1,869 (74%)	839 (70%)	185 (78%)
	Unknown	46 (1%)	38 (2%)	7 (1%)	1 (0%)

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Table 12: SMARTT Age-Specific Language Assessments

	Dynamic		Static		Reference	
	Total N	Mean (S.D.)/ N (%)	Total N	Mean (S.D.)/ N (%)	Total N	Mean (S.D.)/ N (%)
MacArthur Phrases Understood	1484	56.6(27)	169	50.4(27.8)	47	52.6(27.8)
MacArthur Vocabulary Comprehension	1484	47.1(29.9)	169	43.6(29.7)	47	44.7(31.1)
MacArthur Words Production	1484	49.4(21.3)	169	45(21.2)	47	56.3(20)
MacArthur A-E Total Gestures	1484	50.8(28.1)	169	40.6(28.8)	47	55.9(30.9)
Ages and Stages Total Score	1398	44.4(15.3)	268	45(15.7)		.(.)
TELD Receptive Language	37	98.9(16)	285	98.8(14.4)	37	97.8(11.1)
TELD Expressive Language	37	98.9(13.3)	285	99.6(14.7)	37	102.6(10.9)
TELD Spoken Language Quotient	37	95.6(22.6)	285	99.5(17.4)	37	98.1(19.8)
TOLD Spoken Language	541	91.4(13.9)	423	90.1(14.1)	45	87.9(14.3)
TOLD Listening	546	97.1(13.7)	424	94.6(13.6)	45	92(13.4)
TOLD Speaking	545	91.3(14.7)	424	91.6(13.9)	45	90.2(13.6)
TOLD Syntax	544	89(14.2)	424	89.4(14.5)	45	89(13.7)

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Table 13: SMARTT Growth Data at Entry

	Dynamic			Static			Reference		
Score	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Height or Length Z-score	2501	-0.13	1.04	1191	0.31	1.13	235	0.34	1.15
Weight Z-score	2504	-0.57	0.86	1193	0.51	1.25	235	0.20	1.21
BMI Z-score (>= 2 yrs old)	.	.	.	844	0.63	1.30	172	0.08	1.56

BMI is not calculated for children < 2 years.

Z-scores for premature participants are adjusted for newborn and 1-year olds.

Extreme growth Z-scores (> 6 in absolute values) were excluded from calculations and will be queried.

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Table 14: Maternal Substance Use During Pregnancy in Dynamic SMARTT

		Trimester			
		Any Trimester (N=2007)	**First (N=2007)**	**Second (N=2007)**	**Third (N=2007)**
Any Substance Use	Yes	599 (30%)	520 (26%)	332 (17%)	314 (16%)
	No	1,406 (70%)	1,485 (74%)	1,673 (83%)	1,691 (84%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Tobacco	Yes	370 (18%)	349 (17%)	227 (11%)	196 (10%)
	No	1,635 (81%)	1,648 (82%)	1,770 (88%)	1,801 (90%)
	Missing	2 (0%)	10 (0%)	10 (0%)	10 (0%)
Alcohol	Yes	197 (10%)	178 (9%)	53 (3%)	42 (2%)
	No	1,808 (90%)	1,825 (91%)	1,950 (97%)	1,961 (98%)
	Missing	2 (0%)	4 (0%)	4 (0%)	4 (0%)
Marijuana	Yes	180 (9%)	160 (8%)	80 (4%)	61 (3%)
	No	1,825 (91%)	1,842 (92%)	1,922 (96%)	1,941 (97%)
	Missing	2 (0%)	5 (0%)	5 (0%)	5 (0%)
Cocaine	Yes	50 (2%)	39 (2%)	26 (1%)	19 (1%)
	No	1,955 (97%)	1,966 (98%)	1,979 (99%)	1,986 (99%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Antidepressants	Yes	79 (4%)	53 (3%)	35 (2%)	41 (2%)
	No	1,924 (96%)	1,950 (97%)	1,968 (98%)	1,962 (98%)
	Missing	4 (0%)	4 (0%)	4 (0%)	4 (0%)
Pain Medications	Yes	87 (4%)	41 (2%)	43 (2%)	40 (2%)
	No	1,917 (96%)	1,962 (98%)	1,960 (98%)	1,963 (98%)
	Missing	3 (0%)	4 (0%)	4 (0%)	4 (0%)
Methadone	Yes	12 (1%)	11 (1%)	12 (1%)	12 (1%)
	No	1,991 (99%)	1,993 (99%)	1,992 (99%)	1,992 (99%)
	Missing	4 (0%)	3 (0%)	3 (0%)	3 (0%)
Heroin	Yes	10 (0%)	8 (0%)	4 (0%)	2 (0%)
	No	1,994 (99%)	1,996 (99%)	2,000 (100%)	2,002 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Sedative	Yes	10 (0%)	8 (0%)	5 (0%)	4 (0%)
	No	1,994 (99%)	1,996 (99%)	1,999 (100%)	2,000 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Methamphetamines	Yes	11 (1%)	10 (0%)	5 (0%)	1 (0%)
	No	1,994 (99%)	1,995 (99%)	2,000 (100%)	2,004 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Ecstasy	Yes	3 (0%)	3 (0%)	0 (0%)	0 (0%)
	No	2,002 (100%)	2,002 (100%)	2,005 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
PCP	Yes	1 (0%)	1 (0%)	1 (0%)	1 (0%)
	No	2,003 (100%)	2,003 (100%)	2,003 (100%)	2,003 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Opium	Yes	2 (0%)	1 (0%)	1 (0%)	1 (0%)

		Trimester			
		Any Trimester (N=2007)	**First (N=2007)**	**Second (N=2007)**	**Third (N=2007)**
	No	2,003 (100%)	2,004 (100%)	2,004 (100%)	2,004 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Other Drug	Yes	12 (1%)	10 (0%)	7 (0%)	4 (0%)
	No	1,992 (99%)	1,994 (99%)	1,997 (100%)	2,000 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Stimulants	Yes	8 (0%)	5 (0%)	1 (0%)	0 (0%)
	No	1,997 (100%)	2,000 (100%)	2,004 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Barbiturates	Yes	1 (0%)	1 (0%)	0 (0%)	0 (0%)
	No	2,004 (100%)	2,004 (100%)	2,005 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Amphetamines	Yes	1 (0%)	1 (0%)	0 (0%)	0 (0%)
	No	2,004 (100%)	2,004 (100%)	2,005 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Inhalants	Yes	1 (0%)	1 (0%)	1 (0%)	0 (0%)
	No	2,004 (100%)	2,004 (100%)	2,004 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
LSD	No	2,003 (100%)	2,004 (100%)	2,004 (100%)	2,004 (100%)
	Missing	4 (0%)	3 (0%)	3 (0%)	3 (0%)
Other Hallucinogens	Yes	2 (0%)	2 (0%)	1 (0%)	0 (0%)
	No	2,001 (100%)	2,002 (100%)	2,003 (100%)	2,004 (100%)
	Missing	4 (0%)	3 (0%)	3 (0%)	3 (0%)
Ketamine	No	2,005 (100%)	2,005 (100%)	2,005 (100%)	2,005 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)

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Table 15: In Utero ARV Exposure by Birth Year, Static and Dynamic Cohorts Combined

Year of birth	During pregnancy	Labor and delivery only	No ARV during pregnancy labor and delivery	Unknown ARV use	Total
1995	6 (100%)	0 (0%)	0 (0%)	0 (0%)	6 (0%)
1996	33 (89%)	2 (5%)	2 (5%)	0 (0%)	37 (1%)
1997	27 (90%)	1 (3%)	2 (7%)	0 (0%)	30 (1%)
1998	48 (92%)	2 (4%)	0 (0%)	2 (4%)	52 (1%)
1999	66 (93%)	2 (3%)	2 (3%)	1 (1%)	71 (2%)
2000	87 (94%)	1 (1%)	3 (3%)	2 (2%)	93 (3%)
2001	91 (89%)	5 (5%)	4 (4%)	2 (2%)	102 (3%)
2002	98 (94%)	0 (0%)	2 (2%)	4 (4%)	104 (3%)
2003	116 (94%)	0 (0%)	2 (2%)	5 (4%)	123 (3%)
2004	107 (92%)	4 (3%)	3 (3%)	2 (2%)	116 (3%)
2005	122 (96%)	0 (0%)	2 (2%)	3 (2%)	127 (3%)
2006	149 (93%)	3 (2%)	3 (2%)	6 (4%)	161 (4%)
2007	225 (95%)	6 (3%)	1 (0%)	4 (2%)	236 (6%)
2008	338 (95%)	8 (2%)	2 (1%)	6 (2%)	354 (10%)
2009	315 (98%)	1 (0%)	2 (1%)	4 (1%)	322 (9%)
2010	256 (97%)	2 (1%)	0 (0%)	5 (2%)	263 (7%)
2011	260 (99%)	1 (0%)	0 (0%)	1 (0%)	262 (7%)
2012	227 (97%)	1 (0%)	1 (0%)	6 (3%)	235 (6%)
2013	253 (96%)	0 (0%)	2 (1%)	9 (3%)	264 (7%)
2014	238 (93%)	1 (0%)	3 (1%)	13 (5%)	255 (7%)
2015	247 (98%)	1 (0%)	0 (0%)	3 (1%)	251 (7%)
2016	217 (97%)	4 (2%)	2 (1%)	1 (0%)	224 (6%)
Total	3526 (96%)	45 (1%)	38 (1%)	79 (2%)	3688 (100%)

Includes births three months prior to current data download

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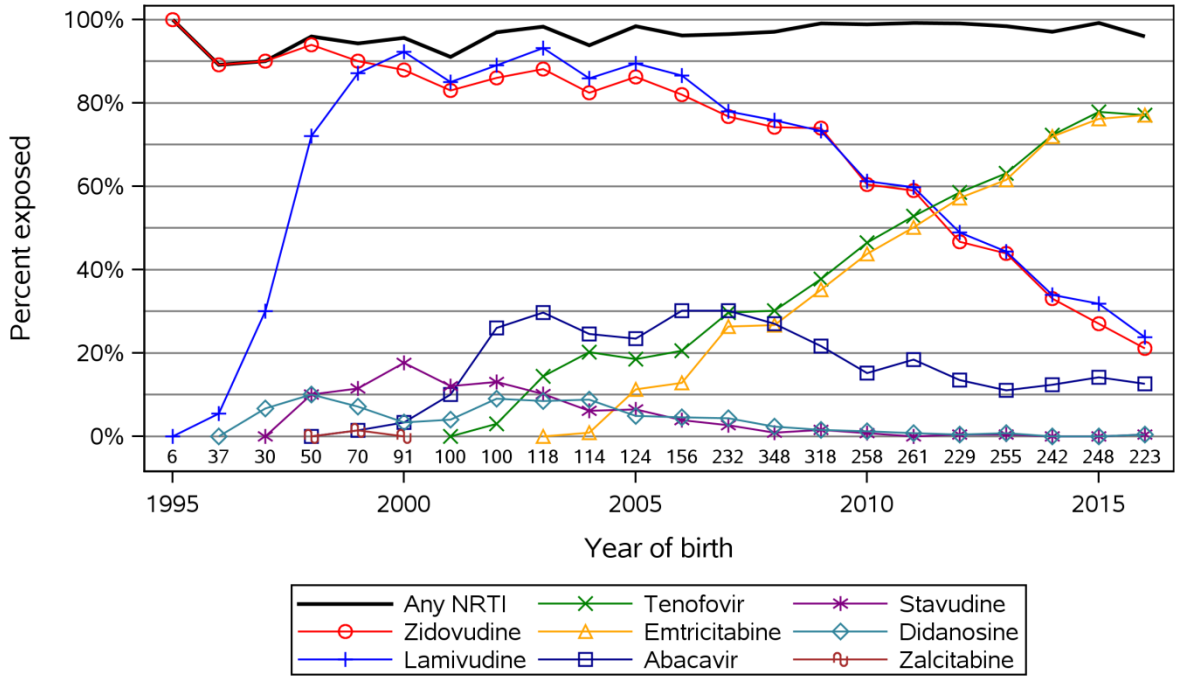
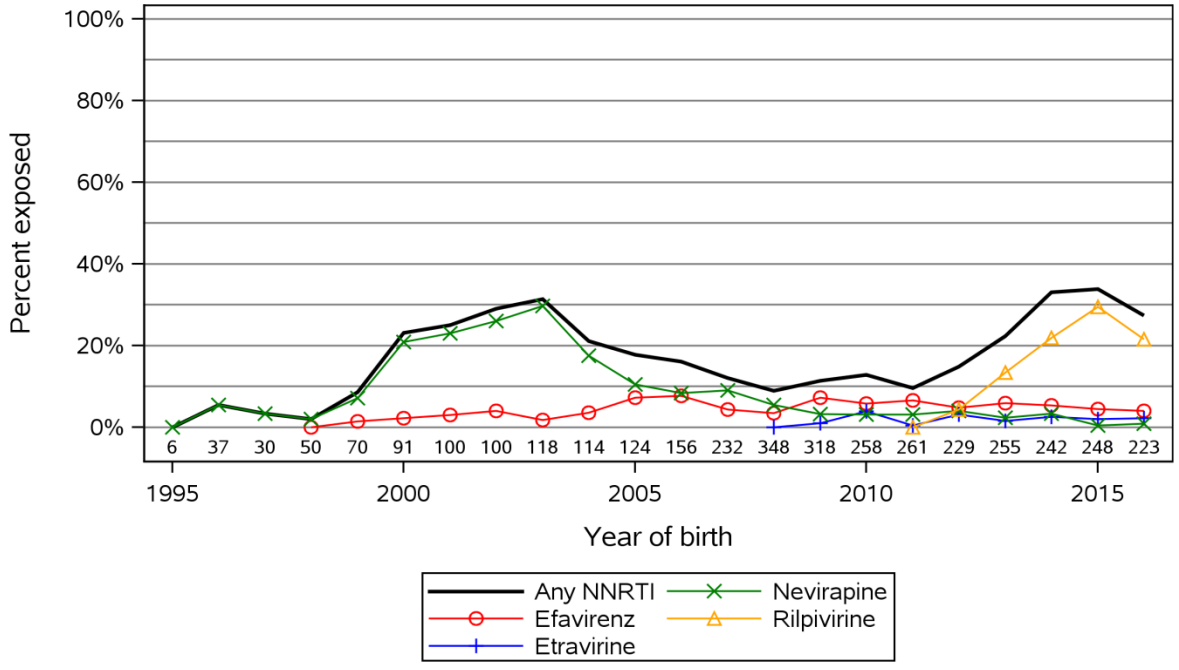
Figure 1: *In Utero* NRTI Exposures by Year of Birth



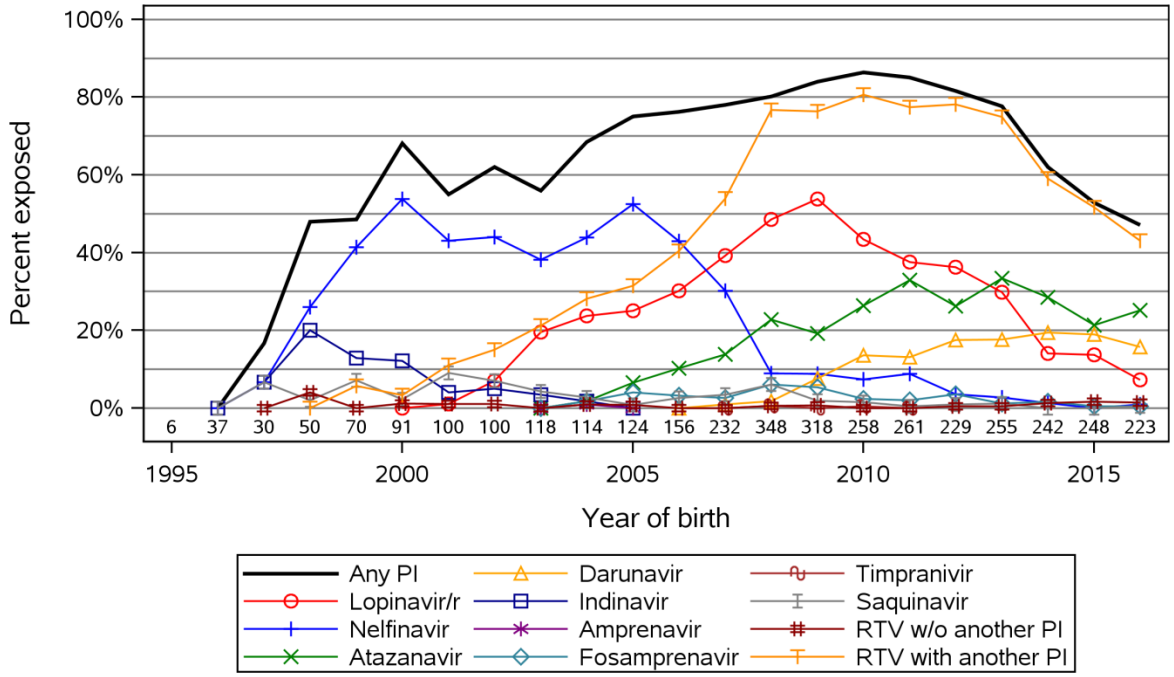
Number above the x-axis represents the number of children with in utero ARV exposure data available

Figure 2: *In Utero* NNRTI Exposures by Year of Birth



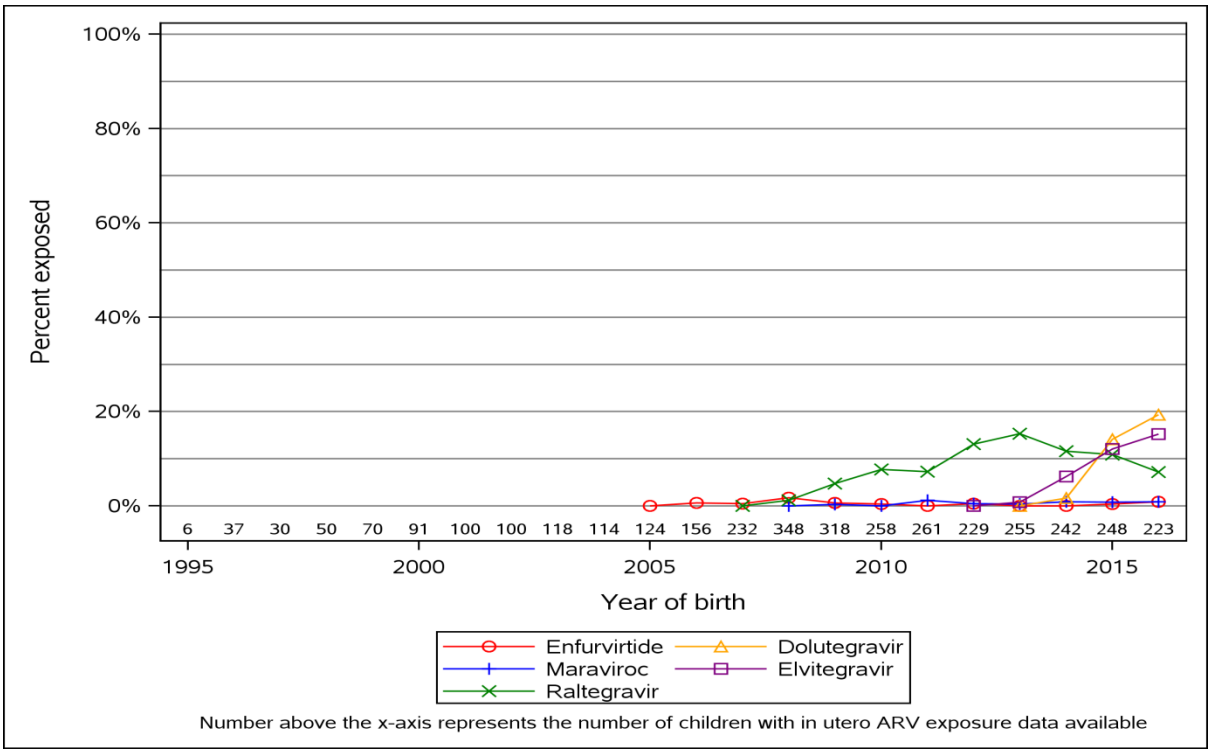
Number above the x-axis represents the number of children with in utero ARV exposure data available

Figure 3: *In Utero* PI Exposures by Year of Birth



Number above the x-axis represents the number of children with in utero ARV exposure data available

Figure 4: *In Utero* FI/II Exposures by Year of Birth



Number above the x-axis represents the number of children with in utero ARV exposure data available

Figure 5: Five Most Common *in Utero* ARV Regimens by Year of Birth