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, 2018, 4289 children and 3278 caregivers enrolled in SMARTT (**Table 1**). As shown in the table, there were 2810 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 (66%), and 30% 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**, 75% of infants were born full-term (≥ 37 weeks gestation) and the majority weighed at least 2500 g (79%). Forty-two percent of infants delivered by spontaneous vaginal delivery, 38% 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, 84% and 67% children are still on study as of the last data retrieval date, respectively; 342 (12%) dynamic and 226 (18%) 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 33 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, 1 drowning, 1 congenital heart disease, 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 scheduled clinic visit for the dynamic and static cohorts were 4.3 and 11.5 years, respectively (**Table 7**). Overall, 97% of the children enrolled completed the entry visit and 88% of visits were done on time or early (**Table 8**). Three children missed the entry visit and 89 (2%) children dropped out of the study before the first study visit.

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

Table 9 summarizes the results of the Bayley Screen for three-year olds. Of the participants assessed, 34-56% 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 49 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**. Among participants who submitted a demographic form at entry visit, 26% of children (25% of dynamic cohort, 29% of static cohort and 21% of reference cohort) had an audiologic exam before enrolling in the study, of whom 8 (1 from dynamic and 7 from the static cohort) were identified with permanent hearing loss in 1 or 2 ears. 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, 760 (29%) 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 3875 children who completed a scheduled study visit, 3686 (95%) were exposed *in utero* to an ARV; 47 (1%) were exposed to ARV during labor and delivery only; while 36 (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 less than 20% in 2017); 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 2001, with use decreasing after 2006; tenofovir disoproxil fumarate (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 80% in 2016, respectively; in addition, TDF and FTC surpassed ZDV and 3TC as the most commonly used NRTI agents in 2012. After 2016 there was a decreasing trend in TDF use meanwhile an increasing trend in tenofovir alafenamide fumarate (TAF) use. 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 before 2009, with use increasing between 1996 and 2003, and decreasing since then (about 1% exposure in 2017); 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 8% in 2017; 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 (or in combination with FTC and TAF as Genvoya since 2016) and increased from 1% to about 23% in 2017; dolutegravir (DTG) use was first reported in 2014 at about 2% and increased to about 23% in 2017. 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 114 months among Static and 57 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=3278)	Dynamic (N=2810)	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 (6%)	51 (2%)	227 (18%)	0 (0%)
	2007 Q4	145 (4%)	51 (2%)	127 (10%)	0 (0%)
	2008 Q1	183 (6%)	79 (3%)	149 (12%)	0 (0%)
	2008 Q2	142 (4%)	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 (3%)	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 (1%)	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 (2%)	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%)

	Cohort			
	Caregiver **(N=3278)**	**Dynamic** **(N=2810)**	**Static** **(N=1240)**	**Reference** **(N=239)**
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 (2%)	0 (0%)	0 (0%)
2015 Q4	44 (1%)	77 (3%)	0 (0%)	0 (0%)
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 (2%)	0 (0%)	0 (0%)
2017 Q2	37 (1%)	56 (2%)	0 (0%)	0 (0%)
2017 Q3	35 (1%)	42 (1%)	0 (0%)	0 (0%)
2017 Q4	32 (1%)	49 (2%)	0 (0%)	0 (0%)
2018 Q1	38 (1%)	54 (2%)	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=4289)	Dynamic (N=2810)	Static (N=1240)	Reference (N=239)
Enrollment site	NYU MEDICAL CTR/BELLEVUE	137 (3%)	79 (3%)	58 (5%)	0 (0%)
	UNIVERSITY OF ALABAMA AT BIRMINGHAM *	194 (5%)	141 (5%)	29 (2%)	24 (10%)
	UNIVERSITY OF SOUTHERN CALIFORNIA	370 (9%)	286 (10%)	84 (7%)	0 (0%)
	SAN JUAN RESEARCH HOSPITAL	136 (3%)	75 (3%)	61 (5%)	0 (0%)
	ST. JUDE CHILDREN'S RESEARCH HOSPITAL *	322 (8%)	254 (9%)	44 (4%)	24 (10%)
	SUNY DOWNSTATE MEDICAL CENTER *	266 (6%)	125 (4%)	119 (10%)	22 (9%)
	UNIV OF COLORADO HEALTH SCIENCES CENTER	222 (5%)	158 (6%)	64 (5%)	0 (0%)
	NEW JERSEY MEDICAL CENTER	114 (3%)	106 (4%)	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) *	144 (3%)	96 (3%)	22 (2%)	26 (11%)
	BRONX/LEBANON HOSPITAL CENTER *	447 (10%)	269 (10%)	137 (11%)	41 (17%)
	UNIVERSITY OF FLORIDA HEALTH SCIENCE CTR	288 (7%)	190 (7%)	98 (8%)	0 (0%)
	UNIVERSITY OF ILLINOIS (CHICAGO) *	229 (5%)	120 (4%)	88 (7%)	21 (9%)
	UNIVERSITY OF PUERTO RICO MEDICAL CENTER	216 (5%)	126 (4%)	90 (7%)	0 (0%)
	CHILDREN'S HOSPITAL OF PHILADELPHIA	27 (1%)	20 (1%)	7 (1%)	0 (0%)
	UNIVERSITY OF MIAMI *	380 (9%)	301 (11%)	40 (3%)	39 (16%)
	TEXAS CHILDREN'S HOSPITAL (BAYLOR) *	251 (6%)	145 (5%)	82 (7%)	24 (10%)
	UNIVERSITY HEALTH SCIENCE CTR (TULANE) *	120 (3%)	91 (3%)	11 (1%)	18 (8%)
	UCSD MEDICAL CENTER	112 (3%)	74 (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	212 (5%)	110 (4%)	102 (8%)	0 (0%)

*Sites with * enrolled 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=4289)	Dynamic (N=2810)	Static (N=1240)	Reference (N=239)
Sex	Male	2169 (51%)	1407 (50%)	643 (52%)	119 (50%)
	Female	2031 (47%)	1314 (47%)	597 (48%)	120 (50%)
	Missing - Form not submitted	89 (2%)	89 (3%)	0 (0%)	0 (0%)
Age* at enrollment (yrs)	Median	4.1	.	4.1	4.7
	Birth, <1**	2839 (66%)	2810 (100%)	29 (2%)	0 (0%)
	1-2	404 (9%)	0 (0%)	352 (28%)	52 (22%)
	3-4	358 (8%)	0 (0%)	291 (23%)	67 (28%)
	5-6	277 (6%)	0 (0%)	206 (17%)	71 (30%)
	7-12	411 (10%)	0 (0%)	362 (29%)	49 (21%)
Race	Asian	21 (0%)	10 (0%)	7 (1%)	4 (2%)
	Native Hawaiian or other Pacific Islander	4 (0%)	3 (0%)	1 (0%)	0 (0%)
	Black or African American	2818 (66%)	1883 (67%)	765 (62%)	170 (71%)
	White	1102 (26%)	693 (25%)	350 (28%)	59 (25%)
	American Indian	7 (0%)	6 (0%)	1 (0%)	0 (0%)
	More than One Race	125 (3%)	102 (4%)	23 (2%)	0 (0%)
	Participant does not want to report	8 (0%)	3 (0%)	4 (0%)	1 (0%)
	Participant does not know	82 (2%)	46 (2%)	32 (3%)	4 (2%)
	Race not available to clinic	122 (3%)	64 (2%)	57 (5%)	1 (0%)
Ethnicity	Hispanic or Latino	1291 (30%)	805 (29%)	432 (35%)	54 (23%)
	Not Hispanic or Latino	2989 (70%)	2000 (71%)	806 (65%)	183 (77%)
	More than one ethnicity	3 (0%)	3 (0%)	0 (0%)	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

** Birth is for dynamic, <1 for static participants

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

Characteristic		Total (N=4289)	Dynamic (N=2810)	Cohort Static (N=1240)	Reference (N=239)
Gestational Age (weeks) at Birth *	< 32	92 (2%)	56 (2%)	31 (3%)	5 (2%)
	32 - < 37	654 (15%)	424 (15%)	205 (17%)	25 (10%)
	≥ 37	3,232 (75%)	2,192 (78%)	860 (69%)	180 (75%)
	Unknown	311 (7%)	138 (5%)	144 (12%)	29 (12%)
Weight at Birth	< 2500 g	701 (16%)	445 (16%)	219 (18%)	37 (15%)
	≥ 2500 g	3,388 (79%)	2,238 (80%)	959 (77%)	191 (80%)
	Unknown	200 (5%)	127 (5%)	62 (5%)	11 (5%)
Mode of Delivery	Spontaneous Vaginal	1,808 (42%)	1,104 (39%)	556 (45%)	148 (62%)
	Assisted Vaginal (Forceps, Vacuum)	72 (2%)	32 (1%)	25 (2%)	15 (6%)
	C-Section Before Labor/Membrane Rupture	1,650 (38%)	1,164 (41%)	449 (36%)	37 (15%)
	C-Section After Labor/Membrane Rupture	539 (13%)	379 (13%)	132 (11%)	28 (12%)
	Unknown Delivery Mode	220 (5%)	131 (5%)	78 (6%)	11 (5%)
Apgar Score at One Minute	< 7	363 (8%)	271 (10%)	92 (7%)	0 (0%)
	≥ 7	3,333 (78%)	2,378 (85%)	955 (77%)	0 (0%)
	Unknown	593 (14%)	161 (6%)	193 (16%)	239 (100%)
Apgar Score at Minute Five	< 7	74 (2%)	57 (2%)	17 (1%)	0 (0%)
	≥ 7	3,625 (85%)	2,594 (92%)	1,031 (83%)	0 (0%)
	Unknown	590 (14%)	159 (6%)	192 (15%)	239 (100%)

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

Missing data are due to either no pregnancy history forms submitted or submission of incomplete form.

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Table 6: SMARTT - Study Status

		Total (N=4289)	Dynamic (N=2810)	Static (N=1240)	Reference (N=239)
				Cohort	
Study status	Still on study	3194 (74%)	2365 (84%)	829 (67%)	0 (0%)
	Completed study	356 (8%)	0 (0%)	125 (10%)	231 (97%)
	Enrollment error / eligibility failure*	11 (0%)	9 (0%)	2 (0%)	0 (0%)
	Death of participant/parent/guardian	33 (1%)	31 (1%)	2 (0%)	0 (0%)
	Withdrawal / loss to follow-up	575 (13%)	342 (12%)	226 (18%)	7 (3%)
	Site closure	108 (3%)	56 (2%)	52 (4%)	0 (0%)
	Other reason	12 (0%)	7 (0%)	4 (0%)	1 (0%)

* 9 Dynamic children in the Enrollment error/eligibility failure category were HIV-infected
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Table 7: SMARTT - Age at Last Scheduled Clinic Visit Among Participants Still on Study

Characteristic		Total (N=3194)	Dynamic (N=2365)	Static (N=829)
			Cohort	
Age (years) at Last Scheduled Clinical Visit	Median (Min, Max)	5.4 (0.0, 21.2)	4.3 (0.0, 10.8)	11.5 (8.8, 21.2)
	0	258 (8%)	258 (11%)	0 (0%)
	1-2	458 (14%)	458 (19%)	0 (0%)
	3-4	484 (15%)	484 (20%)	0 (0%)
	5-6	428 (13%)	428 (18%)	0 (0%)
	7-12	1,165 (36%)	737 (31%)	428 (52%)
	13-15	271 (8%)	0 (0%)	271 (33%)
	>15	130 (4%)	0 (0%)	130 (16%)

* For participants who did not attend the scheduled study visits, the scheduled clinical visit date was used to calculate the age.
For dynamic participants not yet born or just born and study visit form not submitted by the time of data retrieval, the age was set as 0 in above table.
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Table 8: SMARTT - Entry Visit Status

Visit status	Total	Cohort Dynamic	Static	Reference
Visit reported	**4147 (97%)**	**2711 (96%)**	**1200 (97%)**	**236 (99%)**
Early	26 (1%)	1 (0%)	21 (2%)	4 (2%)
In window	3749 (87%)	2547 (91%)	999 (81%)	203 (85%)
Late	372 (9%)	163 (6%)	180 (15%)	29 (12%)
No visit reported	**142 (3%)**	**99 (4%)**	**40 (3%)**	**3 (1%)**
Delinquent	2 (0%)	2 (0%)	0 (0%)	0 (0%)
In window	48 (1%)	48 (2%)	0 (0%)	0 (0%)
Missed visit	3 (0%)	3 (0%)	0 (0%)	0 (0%)
Off study	89 (2%)	46 (2%)	40 (3%)	3 (1%)

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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

			Cohort		
ND Assessment		**Total (N=1330)**	**Dynamic (N=1012)**	**Static (N=275)**	**Reference (N=43)**
Cognitive	At Risk for Devl Delay/Further Eval Needed	49 (3.7%)	38 (3.8%)	11 (4.0%)	0 (0.0%)
	Some Risk for Devl Delay	688 (51.7%)	532 (52.6%)	135 (49.1%)	21 (48.8%)
	Low Risk for Devl Delay	593 (44.6%)	442 (43.7%)	129 (46.9%)	22 (51.2%)
Receptive Communication	At Risk for Devl Delay/Further Eval Needed	30 (2.3%)	19 (1.9%)	11 (4.0%)	0 (0.0%)
	Some Risk for Devl Delay	491 (36.9%)	380 (37.5%)	97 (35.3%)	14 (32.6%)
	Low Risk for Devl Delay	806 (60.6%)	610 (60.3%)	167 (60.7%)	29 (67.4%)
	Not Done	3 (0.2%)	3 (0.3%)	0 (0.0%)	0 (0.0%)
Expressive Communication	At Risk for Devl Delay/Further Eval Needed	47 (3.5%)	38 (3.8%)	9 (3.3%)	0 (0.0%)
	Some Risk for Devl Delay	540 (40.6%)	422 (41.7%)	108 (39.3%)	10 (23.3%)
	Low Risk for Devl Delay	738 (55.5%)	547 (54.1%)	158 (57.5%)	33 (76.7%)
	Not Done	5 (0.4%)	5 (0.5%)	0 (0.0%)	0 (0.0%)
Fine Motor	At Risk for Devl Delay/Further Eval Needed	30 (2.3%)	22 (2.2%)	8 (2.9%)	0 (0.0%)
	Some Risk for Devl Delay	509 (38.3%)	406 (40.1%)	91 (33.1%)	12 (27.9%)
	Low Risk for Devl Delay	788 (59.2%)	581 (57.4%)	176 (64.0%)	31 (72.1%)
	Not Done	3 (0.2%)	3 (0.3%)	0 (0.0%)	0 (0.0%)
Gross Motor	At Risk for Devl Delay/Further Eval Needed	23 (1.7%)	17 (1.7%)	6 (2.2%)	0 (0.0%)
	Some Risk for Devl Delay	407 (30.6%)	322 (31.8%)	78 (28.4%)	7 (16.3%)
	Low Risk for Devl Delay	896 (67.4%)	669 (66.1%)	191 (69.5%)	36 (83.7%)
	Not Done	4 (0.3%)	4 (0.4%)	0 (0.0%)	0 (0.0%)

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Table 10: Age-specific ND Assessments

| ND Assessment | Score | Cohort | | | | | |
| | | Dynamic | | Static | | Reference | |
		N	Mean (S.D)	N	Mean (S.D)	N	Mean (S.D)
Bayley-III (1 year old)	Cognitive, Composite	1454	103.0 (14.1)	146	102.9 (15.2)	49	102.2 (14.0)
	Language, Composite	1452	94.8 (13.6)	145	93.2 (14.7)	49	95.1 (12.5)
	Motor, Composite	1446	97.4 (12.7)	145	96.9 (15.9)	49	100.9 (14.7)
	Social-Emotional, Composite	1415	101.8 (17.6)	142	101.6 (18.5)	49	100.5 (16.4)
	General Adaptive, Composite	1412	94.9 (14.4)	142	93.4 (15.0)	49	92.3 (11.3)
WPPSI (5 years old)	Full Scale IQ	692	94.4 (15.2)	445	94.6 (14.5)	47	93.6 (15.6)
	Performance IQ	707	96.3 (15.4)	447	97.3 (15.2)	47	95.6 (15.3)
	Verbal IQ	704	92.4 (14.4)	447	92.1 (12.9)	47	91.6 (13.9)
	Processing Speed IQ	676	95.2 (15.6)	442	96.3 (15.9)	47	95.0 (15.4)
	General Language IQ	420	93.0 (13.4)	210	91.0 (14.1)	19	91.1 (11.4)
WASI (7+ odd years old)*	Full Scale IQ	148	100.4 (15.3)	781	97.9 (14.0)	48	100.8 (12.6)
	Performance IQ	148	96.2 (13.4)	781	95.2 (13.1)	49	95.3 (13.0)
	Verbal IQ	148	104.5 (18.5)	781	101.0 (16.0)	48	105.8 (14.2)
WIAT (7+ odd years old)*	Word Reading, Standard Score	147	99.1 (16.9)	779	97.3 (16.1)	49	97.1 (15.0)
	Spelling, Standard Score	146	98.5 (17.8)	776	97.8 (16.5)	48	98.8 (15.8)
	Numerical Operations, Standard Score	146	93.8 (16.8)	779	94.0 (16.6)	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

			Cohort		
Characteristic		**Total (N=4132)**	**Dynamic (N=2701)**	**Static (N=1195)**	**Reference (N=236)**
Concerns about hearing?	Yes	125 (3%)	39 (1%)	77 (6%)	9 (4%)
	No	3,962 (96%)	2,625 (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	3,963 (96%)	2,664 (99%)	1,086 (91%)	213 (90%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Child failed hearing screening?	Yes	145 (4%)	69 (3%)	65 (5%)	11 (5%)
	No	3,942 (95%)	2,595 (96%)	1,123 (94%)	224 (95%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Child tested by audiologist?	Yes	1,085 (26%)	686 (25%)	349 (29%)	50 (21%)
	No	3,002 (73%)	1,978 (73%)	839 (70%)	185 (78%)
	Unknown	45 (1%)	37 (1%)	7 (1%)	1 (0%)
Perm hearing loss in 1-2 ears?	Yes	8 (0%)	1 (0%)	7 (1%)	0 (0%)
	No	1,076 (26%)	684 (25%)	342 (29%)	50 (21%)
	Test not done	3,002 (73%)	1,978 (73%)	839 (70%)	185 (78%)
	Unknown	46 (1%)	38 (1%)	7 (1%)	1 (0%)

Table 12: SMARTT Age-Specific Language Assessments

Language Assessment		Dynamic		Static		Reference	
		Total N	Mean (S.D.)	Total N	Mean (S.D.)	Total N	Mean (S.D.)
MacArthur	Phrases Understood	1630	56.4 (27.4)	169	50.4 (27.8)	47	52.6 (27.8)
	Vocabulary Comprehension	1630	46.8 (29.9)	169	43.6 (29.7)	47	44.7 (31.1)
	Words Production	1630	49.3 (21.5)	169	45 (21.2)	47	56.3 (20)
	A-E Total Gestures	1630	50.3 (28.2)	169	40.6 (28.8)	47	55.9 (30.9)
Ages and Stages	Total Score	1559	44.4 (15.3)	269	45.1 (15.7)		. (.)
TELD	Receptive Language	37	98.9 (16)	286	98.8 (14.4)	37	97.8 (11.1)
	Expressive Language	37	98.9 (13.3)	286	99.6 (14.7)	37	102.6 (10.9)
	Spoken Language Quotient	37	95.6 (22.6)	286	99.5 (17.4)	37	98.1 (19.8)
TOLD	Spoken Language	652	91.8 (14.5)	423	90.1 (14.1)	45	87.9 (14.3)
	Listening	657	97.3 (14.3)	424	94.6 (13.6)	45	92 (13.4)
	Speaking	656	91.8 (15)	424	91.6 (13.9)	45	90.2 (13.6)
	Syntax	655	89.2 (14.5)	424	89.4 (14.5)	45	89 (13.7)

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Table 13: SMARTT Growth Data at Entry

Score	Dynamic			Static			Reference		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Height or Length Z-score	2685	-0.12	1.03	1191	0.31	1.13	235	0.34	1.15
Weight Z-score	2689	-0.57	0.85	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 SMARTT Dynamic Cohort

		Trimester			
		Any Trimester (N=2648)	First (N=2648)	Second (N=2648)	Third (N=2648)
Any Substance Use	Yes	779 (29%)	673 (25%)	433 (16%)	405 (15%)
	No	1,867 (71%)	1,973 (75%)	2,213 (84%)	2,241 (85%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Tobacco	Yes	478 (18%)	449 (17%)	299 (11%)	253 (10%)
	No	2,168 (82%)	2,186 (83%)	2,336 (88%)	2,382 (90%)
	Missing	2 (0%)	13 (0%)	13 (0%)	13 (0%)
Alcohol	Yes	250 (9%)	225 (8%)	67 (3%)	52 (2%)
	No	2,396 (90%)	2,419 (91%)	2,577 (97%)	2,592 (98%)
	Missing	2 (0%)	4 (0%)	4 (0%)	4 (0%)
Marijuana	Yes	236 (9%)	210 (8%)	106 (4%)	81 (3%)
	No	2,410 (91%)	2,432 (92%)	2,536 (96%)	2,561 (97%)
	Missing	2 (0%)	6 (0%)	6 (0%)	6 (0%)
Cocaine	Yes	63 (2%)	51 (2%)	36 (1%)	25 (1%)
	No	2,583 (98%)	2,595 (98%)	2,610 (99%)	2,621 (99%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Antidepressants	Yes	104 (4%)	69 (3%)	51 (2%)	55 (2%)
	No	2,540 (96%)	2,575 (97%)	2,593 (98%)	2,589 (98%)
	Missing	4 (0%)	4 (0%)	4 (0%)	4 (0%)
Pain Medications	Yes	123 (5%)	52 (2%)	63 (2%)	59 (2%)
	No	2,521 (95%)	2,592 (98%)	2,581 (97%)	2,585 (98%)
	Missing	4 (0%)	4 (0%)	4 (0%)	4 (0%)
Methadone	Yes	16 (1%)	13 (0%)	15 (1%)	16 (1%)
	No	2,627 (99%)	2,632 (99%)	2,630 (99%)	2,629 (99%)
	Missing	5 (0%)	3 (0%)	3 (0%)	3 (0%)
Heroin	Yes	13 (0%)	10 (0%)	6 (0%)	4 (0%)
	No	2,632 (99%)	2,635 (100%)	2,639 (100%)	2,641 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Sedative	Yes	13 (0%)	8 (0%)	6 (0%)	5 (0%)
	No	2,632 (99%)	2,637 (100%)	2,639 (100%)	2,640 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Methamphetamines	Yes	13 (0%)	12 (0%)	6 (0%)	3 (0%)
	No	2,633 (99%)	2,634 (99%)	2,640 (100%)	2,643 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)

| | | **Trimester** | | | |
		Any Trimester (N=2648)	**First (N=2648)**	**Second (N=2648)**	**Third (N=2648)**
Ecstasy	Yes	3 (0%)	3 (0%)	0 (0%)	0 (0%)
	No	2,643 (100%)	2,643 (100%)	2,646 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
PCP	Yes	2 (0%)	2 (0%)	1 (0%)	1 (0%)
	No	2,643 (100%)	2,643 (100%)	2,644 (100%)	2,644 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Opium	Yes	4 (0%)	2 (0%)	3 (0%)	3 (0%)
	No	2,642 (100%)	2,644 (100%)	2,643 (100%)	2,643 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Other Drug	Yes	15 (1%)	11 (0%)	8 (0%)	7 (0%)
	No	2,630 (99%)	2,634 (99%)	2,637 (100%)	2,638 (100%)
	Missing	3 (0%)	3 (0%)	3 (0%)	3 (0%)
Stimulants	Yes	7 (0%)	5 (0%)	0 (0%)	0 (0%)
	No	2,639 (100%)	2,641 (100%)	2,646 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Barbiturates	Yes	1 (0%)	1 (0%)	0 (0%)	0 (0%)
	No	2,645 (100%)	2,645 (100%)	2,646 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Amphetamines	Yes	1 (0%)	1 (0%)	0 (0%)	0 (0%)
	No	2,645 (100%)	2,645 (100%)	2,646 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
Inhalants	Yes	1 (0%)	1 (0%)	1 (0%)	0 (0%)
	No	2,645 (100%)	2,645 (100%)	2,645 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)
LSD	No	2,643 (100%)	2,645 (100%)	2,645 (100%)	2,645 (100%)
	Missing	5 (0%)	3 (0%)	3 (0%)	3 (0%)
Other Hallucinogens	Yes	2 (0%)	2 (0%)	1 (0%)	0 (0%)
	No	2,641 (100%)	2,642 (100%)	2,643 (100%)	2,644 (100%)
	Missing	5 (0%)	4 (0%)	4 (0%)	4 (0%)
Ketamine	No	2,646 (100%)	2,646 (100%)	2,646 (100%)	2,646 (100%)
	Missing	2 (0%)	2 (0%)	2 (0%)	2 (0%)

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 (2%)
2001	91 (89%)	5 (5%)	4 (4%)	2 (2%)	102 (3%)
2002	97 (93%)	0 (0%)	2 (2%)	5 (5%)	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	121 (95%)	0 (0%)	2 (2%)	4 (3%)	127 (3%)
2006	146 (91%)	3 (2%)	3 (2%)	9 (6%)	161 (4%)
2007	218 (92%)	6 (3%)	1 (0%)	11 (5%)	236 (6%)
2008	330 (93%)	8 (2%)	2 (1%)	14 (4%)	354 (9%)
2009	315 (98%)	1 (0%)	2 (1%)	4 (1%)	322 (8%)
2010	254 (97%)	2 (1%)	0 (0%)	7 (3%)	263 (7%)
2011	260 (99%)	1 (0%)	0 (0%)	1 (0%)	262 (7%)
2012	222 (94%)	1 (0%)	1 (0%)	11 (5%)	235 (6%)
2013	252 (95%)	1 (0%)	2 (1%)	9 (3%)	264 (7%)
2014	238 (93%)	1 (0%)	3 (1%)	13 (5%)	255 (7%)
2015	248 (99%)	1 (0%)	0 (0%)	2 (1%)	251 (6%)
2016	223 (99%)	2 (1%)	0 (0%)	0 (0%)	225 (6%)
2017	181 (97%)	3 (2%)	0 (0%)	2 (1%)	186 (5%)
Total	3686 (95%)	47 (1%)	36 (1%)	106 (3%)	3875 (100%)

Includes participants who were born at least three months prior to current data download
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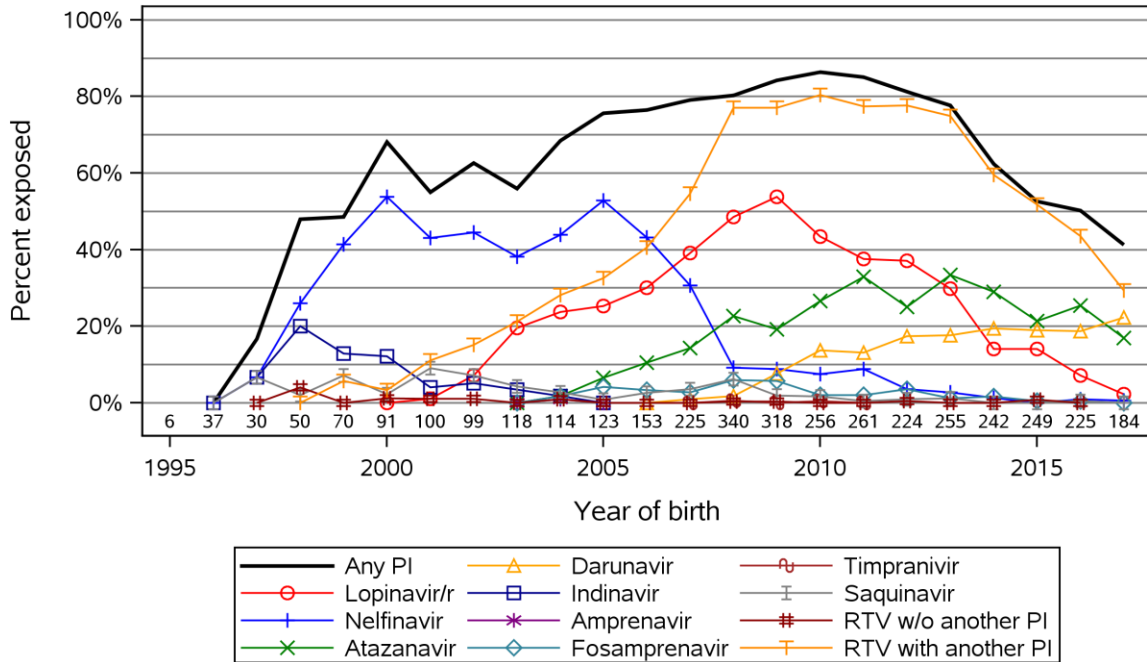**Figure 1: *In Utero* NRTI Exposures by Year of Birth**
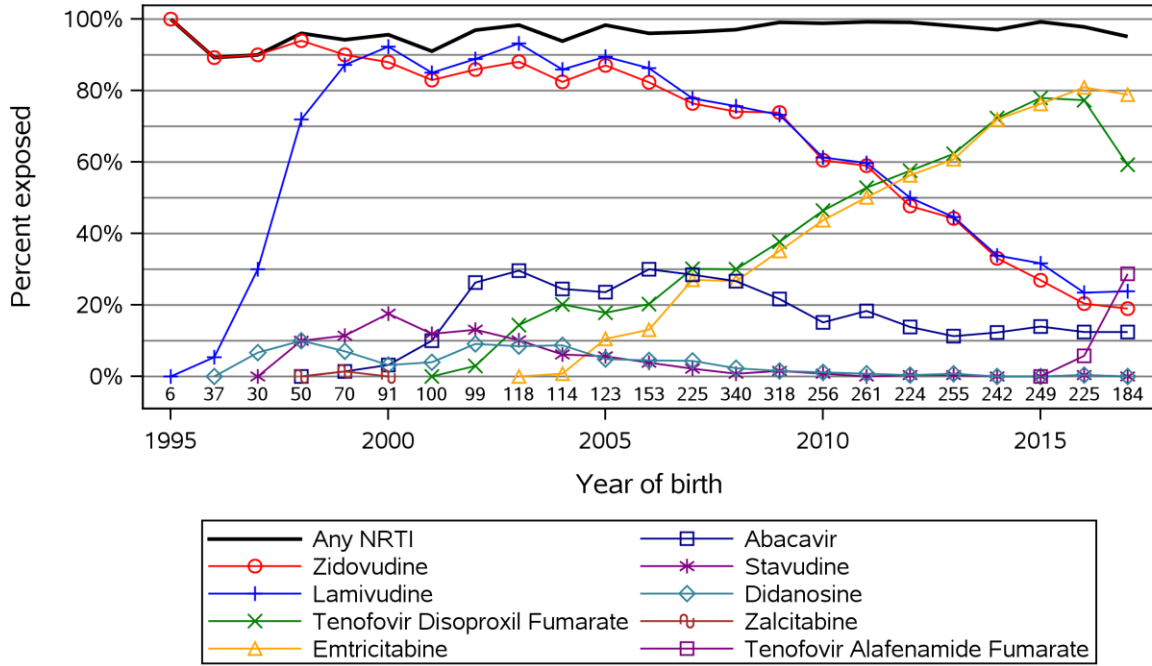
Number above the x-axis represents the number of children with in utero ARV exposure data available
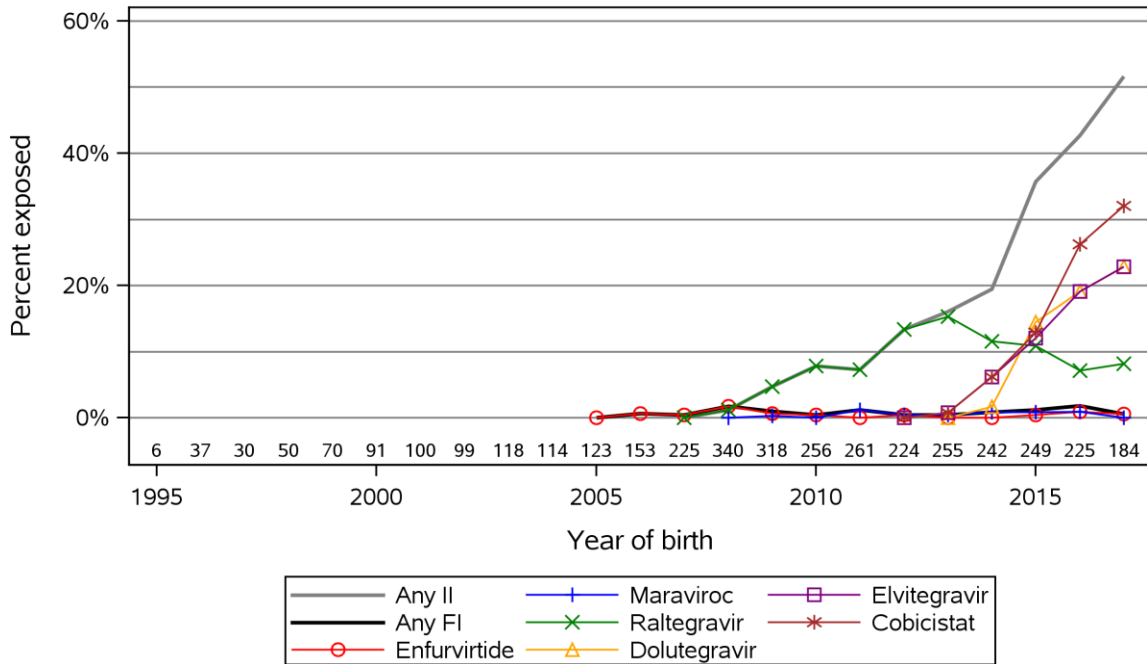
Figure 2: *In Utero* NNRTI Exposures by Year of Birth
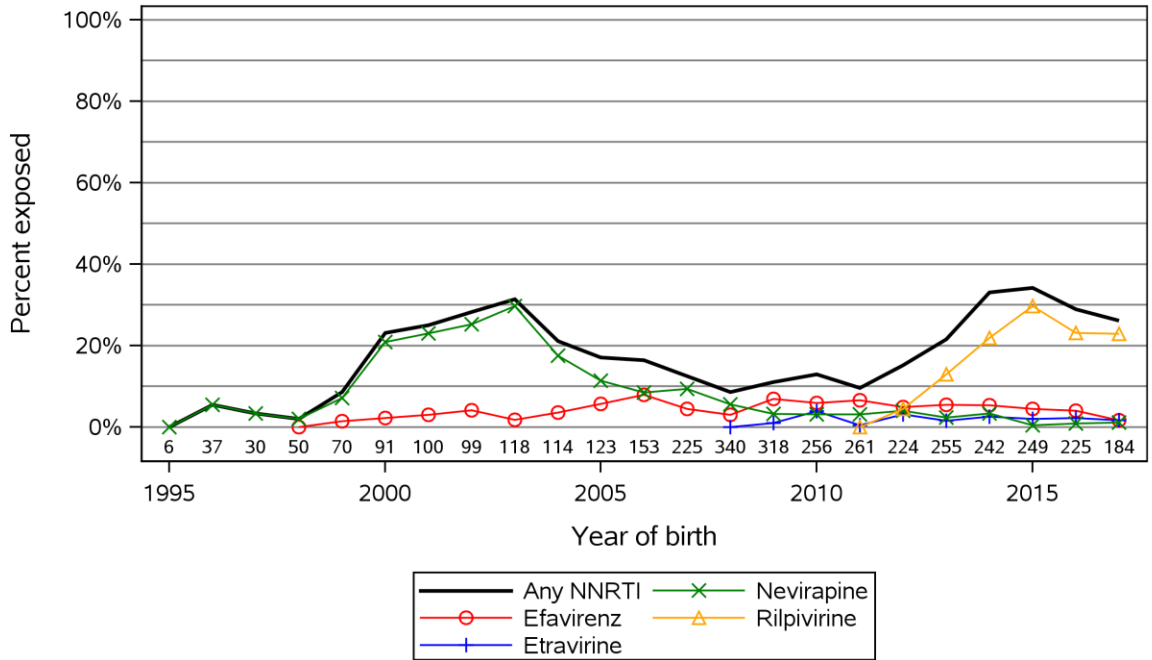
Number above the x-axis represents the number of children with in utero ARV exposure data available

**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

Number of in utero ARV regimens with duration at least 3 days
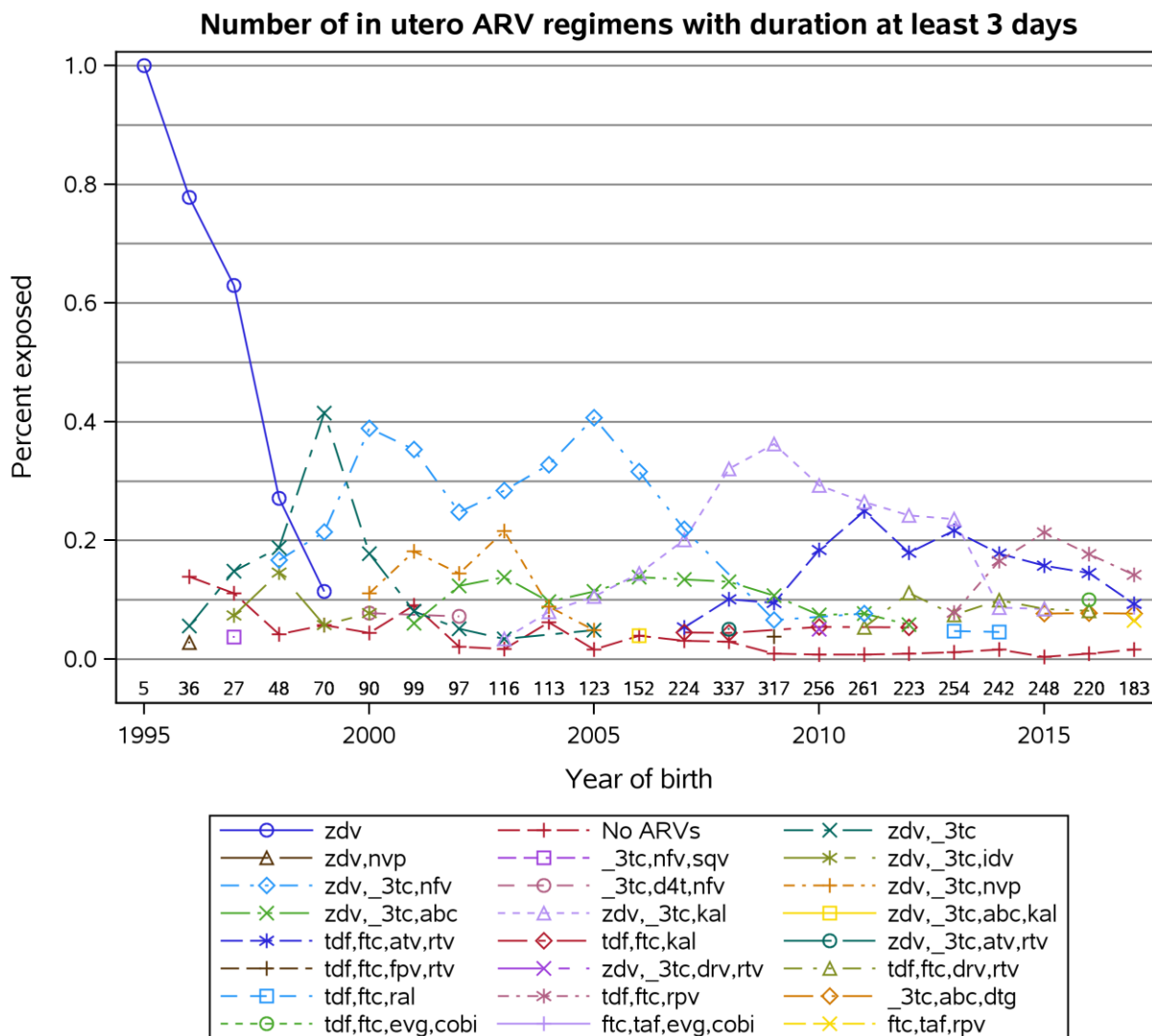
Number above the x-axis represents the number of children with detailed timing of in utero ARV exposure available

Figures 1 to 5 were created by: /home/phacs/actgPH100/monitoring/detlprogs/arvfigs.sas