Prenatal timing of antiretroviral therapy initiation and early developmental and growth outcomes among HIV-exposed, uninfected preschool-aged children in Tanzania

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Disclosures: None

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WORLD CONGRESS OF EPIDEMIOLOGY 2024

With increasing HIV prophylaxis availability and focus on prevention, vertical transmission of HIV has declined

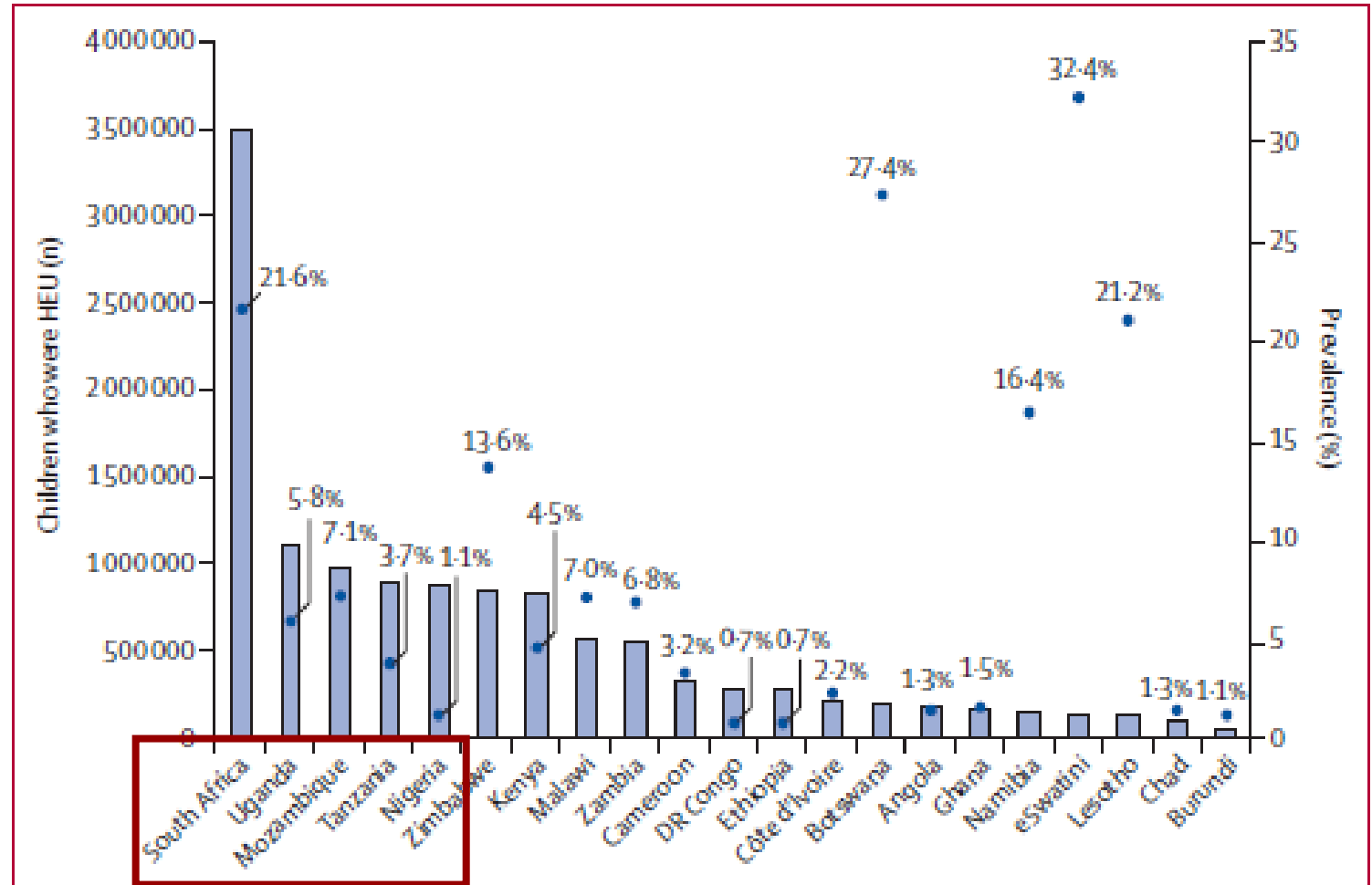**HIV prophylaxis recommended as soon as possible at diagnosis**

Figure 2: 2019 UNAIDS estimates of absolute number and prevalence of children who were HEU (aged 0–14 years) in the 21 countries with the highest burden of HIV in 2018

Slogrove et al. Lancet Global Health; 2020;8: e67–75

Children who are born to women living with HIV are at greater risk of developmental delay as compared to their HIV-unexposed peers

Maternal HIV +/- ART exposure
- Direct exposure to HIV virions and viral proteins
- Maternal immune activation / inflammation
- Fetal and infant immune activation / inflammation
- ART toxicity
- *As yet unknown*

Macrosystem & microsystem

ENVIRONMENT (water, sanitation & hygiene)

POVERTY (socioeconomic determinants)

FAMILY (parental education, age, household)

Common risk factors
- Exposure to intrauterine infections (e.g. CMV, rubella)
- Exposure to toxins (alcohol, smoking, air pollution, mycotoxins)
- Adverse birth outcomes
- Suboptimal breastfeeding
- Inadequate diet
- Childhood illness
- Maternal morbidity and mortality
- Maternal mental health

Mechanisms
- Opportunistic infections
- Dysbiotic gut microbiome and enteropathy
- Iron deficiency anaemia
- Genetic vulnerabilities & epigenetic changes
- Malnutrition
- Toxic stress
- Inflammation
- Growth hormone axis disruption
- Reduced mother-child interaction
- Atypical brain development

Outcome

Poor childhood growth & development

Pregnancy: Fetal growth & development

Early child growth & development

Late childhood: School outcomes & growth

Adolescence: Health & cognition

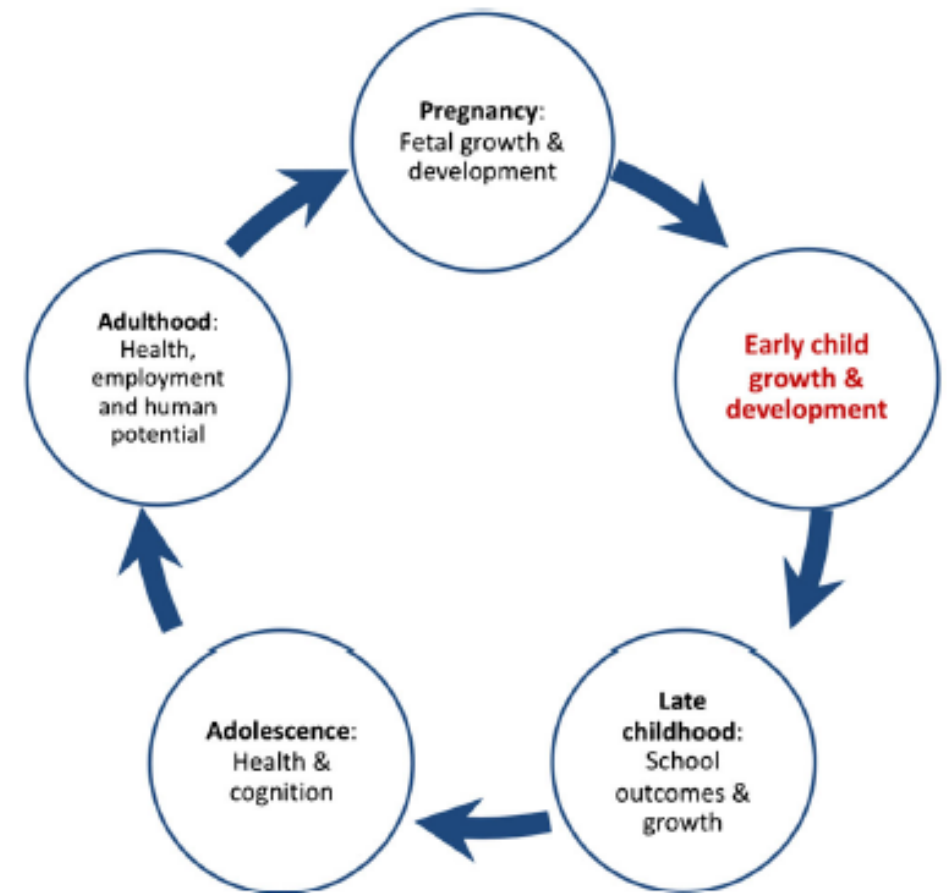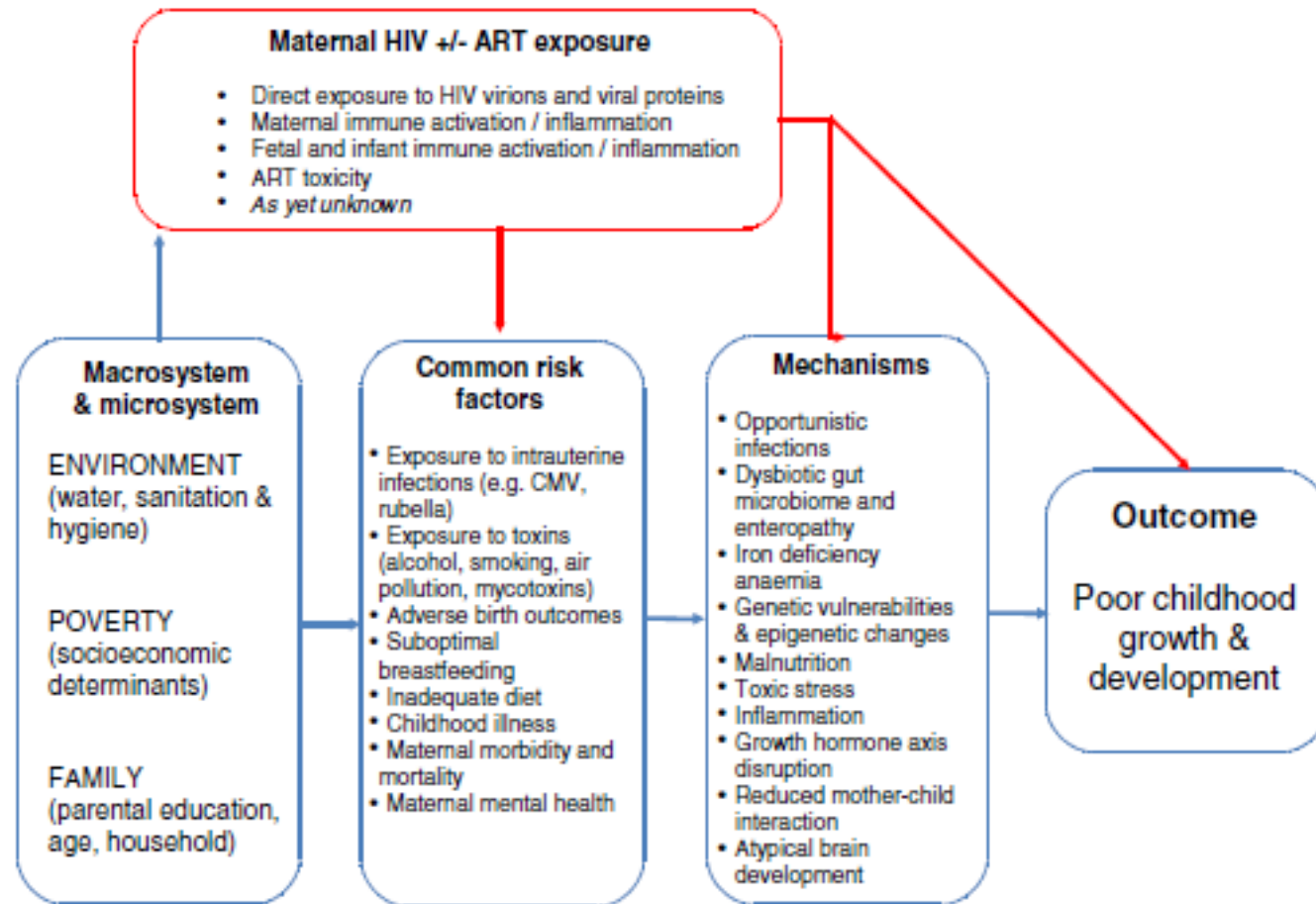Adulthood: Health, employment and human potential

Fig. 1 The cycle of child growth and development

We followed a cohort of children born to women living with HIV who were previously enrolled in a randomized controlled trial in Tanzania

Pregnant women in the parent trial were either previously on, or initiated, cART at trial enrolment between 12-27 weeks of gestational age.

Children were 3-6 years of age at assessment

Maternal and child health and nutrition, and other measures

- The parent trial collected detailed information about maternal health in pregnancy and newborn outcomes up to 1-year postpartum.

- We collected data on the mothers and child's current health, anthropometric status (height/weight), dietary intake, and morbidities (diarrhea, fever, etc.) in the follow-up study.

- Other measures included at follow-up:
  - Disciplinary practices, including corporal punishment, using the Family Care Indicators;
  - Maternal/caregiver mental health, social support, etc.;
  - Children's learning environments
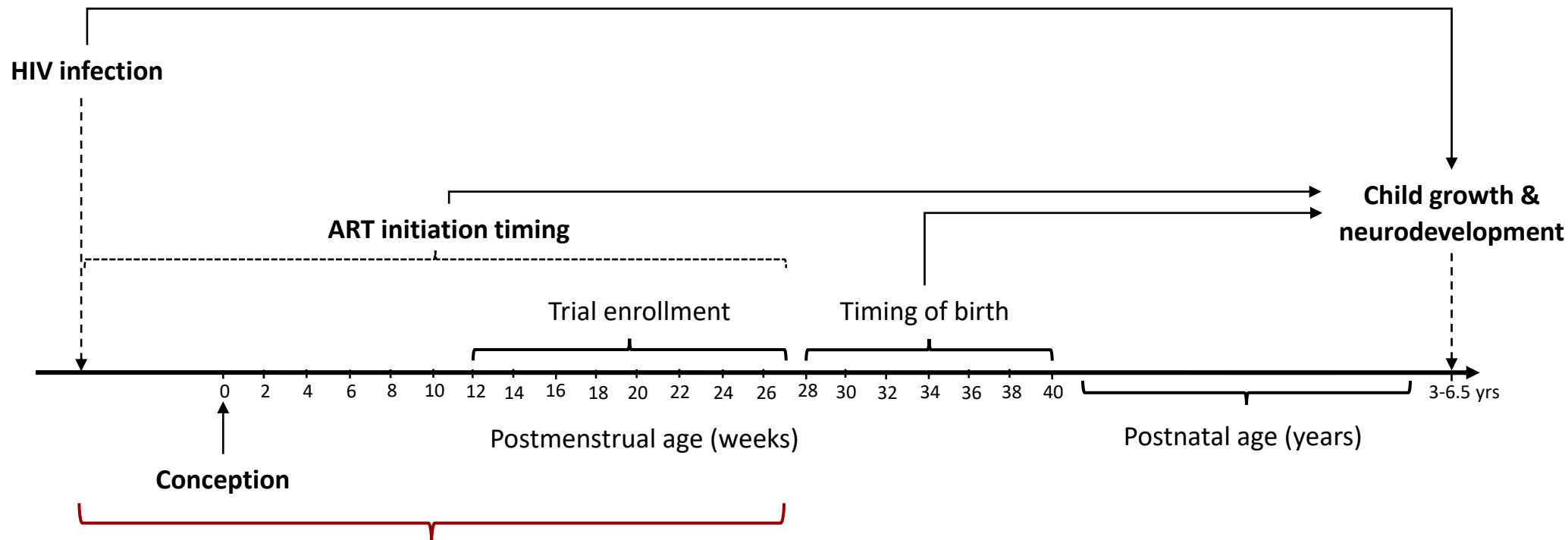
Photos taken with consent.

Measuring child development and school readiness

- We used the **International Development and Early Learning Assessment (IDELA)** tool to assess neurodevelopmental outcomes and school readiness.

- IDELA is a rigorous, culturally adaptable, and open-source instrument that can be used to directly assess 5 core child development domains:
  (1) motor skills,
  (2) language and early literacy,
  (3) math and problem solving,
  (4) social-emotional development,
  (5) executive functioning (i.e., memory, inhibitory control, sustained attention).
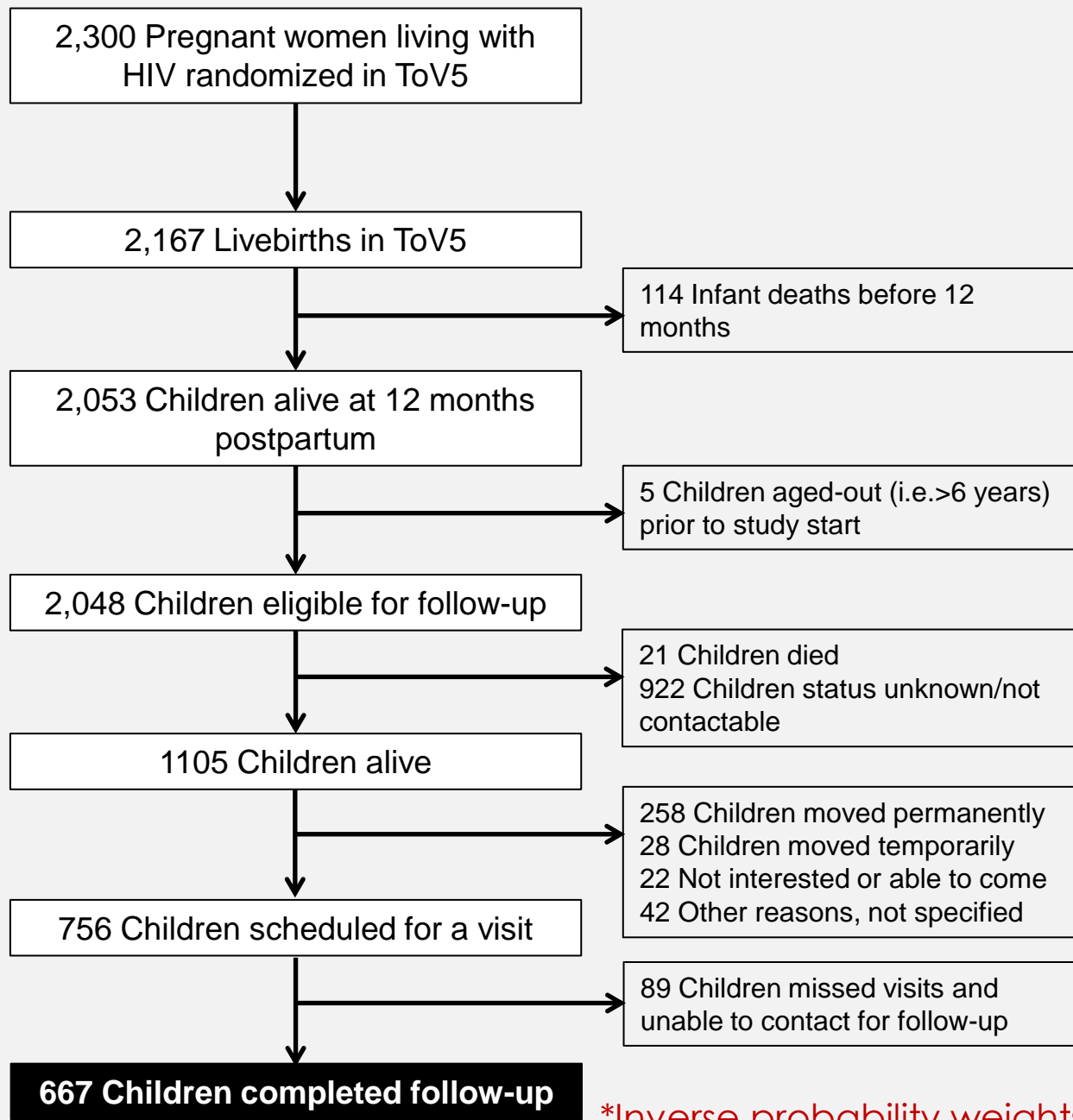
Variation in the timing of exposure (cART) initiation

Flowchart

2,300 Pregnant women living with HIV randomized in ToV5

↓

2,167 Livebirths in ToV5

→ 114 Infant deaths before 12 months

↓

2,053 Children alive at 12 months postpartum

→ 5 Children aged-out (i.e.>6 years) prior to study start

↓

2,048 Children eligible for follow-up

→ 21 Children died
922 Children status unknown/not contactable

↓

1105 Children alive

→ 258 Children moved permanently
28 Children moved temporarily
22 Not interested or able to come
42 Other reasons, not specified

↓

756 Children scheduled for a visit

→ 89 Children missed visits and unable to contact for follow-up

↓

**667 Children completed follow-up**

*Inverse probability weights

Table

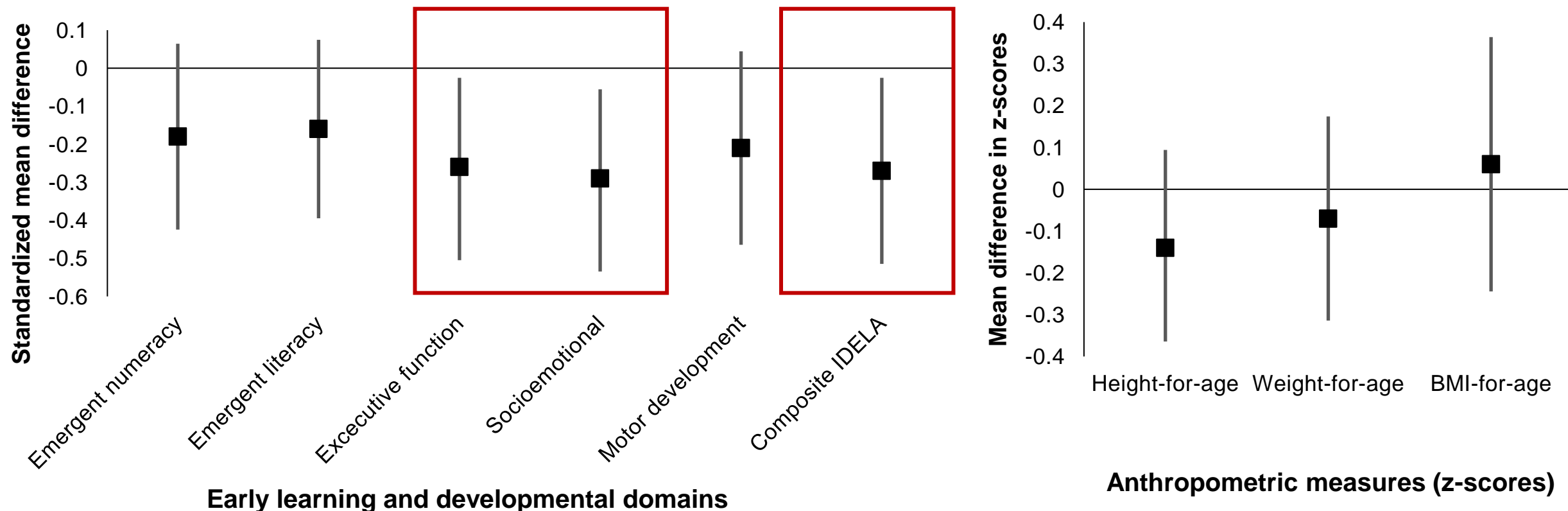| Characteristics	Mothers eligible for enrolment (n = 2167)	Mothers enrolled in the follow-up study (n = 667)
Maternal age (years)		
18-24	344 (15.9)	71 (10.6)
25-34	1263 (58.3)	369 (55.3)
≥35	560 (25.8)	227 (34.0)
Maternal education		
No formal education	242 (11.2)	65 (9.76)
Primary	1266 (58.5)	397 (59.6)
Secondary	506 (23.4)	162 (24.3)
Advanced	151 (6.97)	42 (6.31)
Marital status[2]		
Married or Cohabiting	1640 (75.8)	536 (80.5)
Single	463 (21.4)	111 (16.7)
Widowed or divorced	59 (2.73)	18 (2.70)
Parity		
≤1	726 (33.5)	198 (29.7)
2-3	827 (38.2)	300 (45.1)
≥4	612 (28.3)	168 (25.2)
Maternal CD4 T-cell count (cells/mL^3)		
<350	444 (20.5)	127 (19.0)
350-500	287 (13.2)	96 (14.4)
≥500	285 (13.2)	88 (13.2)
WHO HIV disease stage		
I	1855 (85.6)	546 (81.9)
II	133 (6.14)	48 (7.20)
III	161 (7.43)	65 (9.75)
IV	18 (0.83)	8 (1.20)
cART Regimen		
Tenofovir (TDF), Lamivudine (3TC), Efavirenz (EFV)	2141 (98.8)	662 (99.3)
Other	23 (1.06)	5 (0.75)

No differences in growth and early learning outcomes among children born to women who initiated <u>cART preconceptionally</u> compared during pregnancy
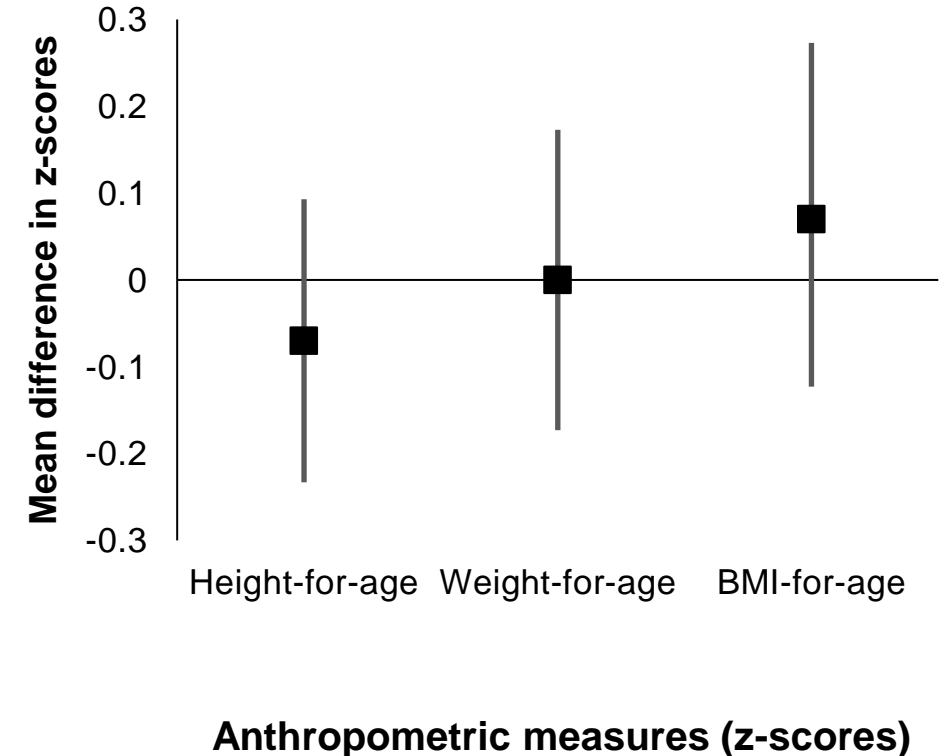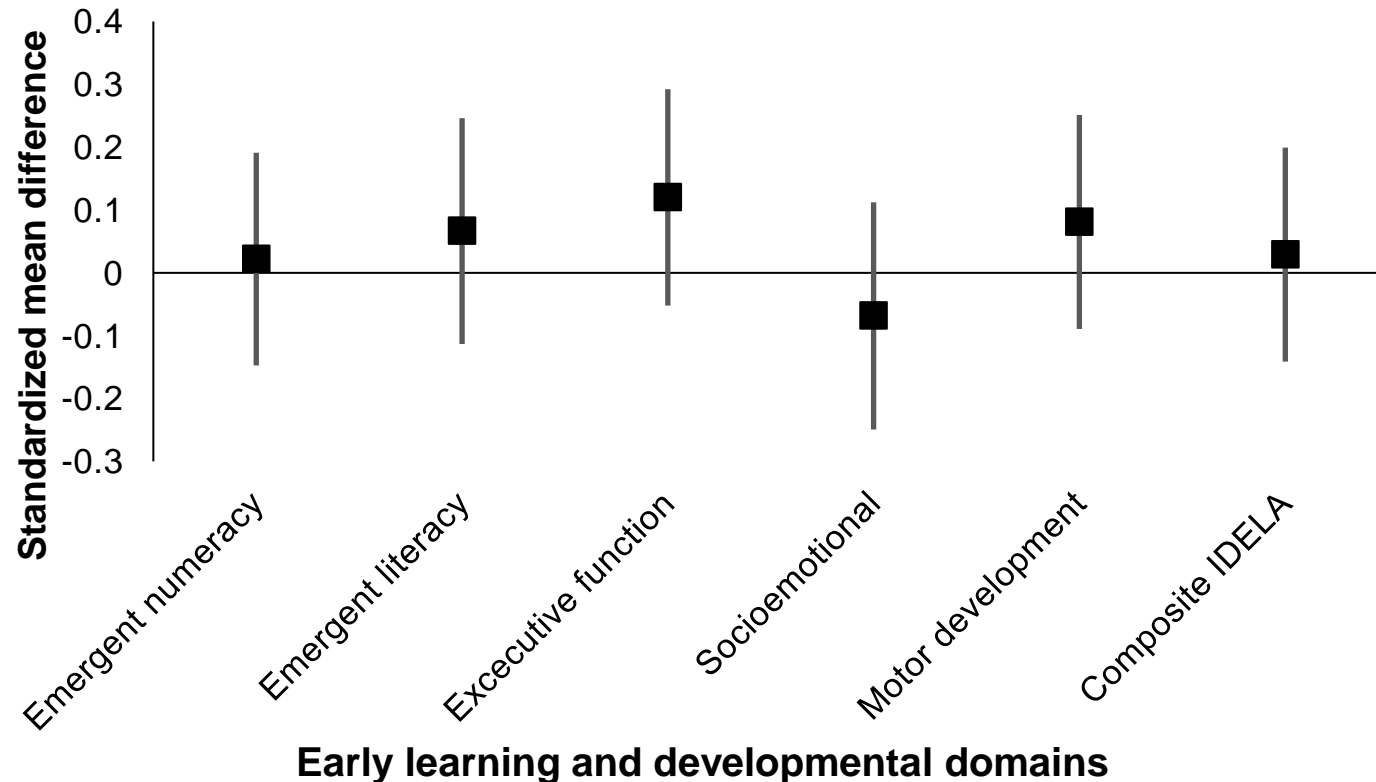
*Marginal models with inverse probability weights. Covariates accounted for in the marginal models included: child sex, maternal CD4 T cell count (<350, 350-500, ≥500 cells/µl), WHO disease stage (1,2,3,4), self-reported history of hypertension, any alcohol use (in the last month), body mass index at randomization (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m2), parity (0-1, 2-3, 4+), maternal age (18-24, 25-34, ≥35 years), maternal education (no formal education, primary, secondary, advanced), marital status (married, cohabitating, single), wealth quintile, clinic site, and whether mothers received vitamin D or placebo during pregnancy.

Children born to women who initiated cART during pregnancy at <u>≤20 weeks</u> compared to ≥20 weeks gestational age,

Discussion of findings

- Children born to women who initiated cART preconceptionally had similar growth and early learning and developmental outcomes compared to children born to women who started ART during pregnancy.

- Among women who started cART during pregnancy, children born to women who initiated cART at <20 weeks had lower socio-emotional and executive function scores compared to those born to women who initiated between 20-27 weeks of GA; but no differences in growth.
  - Effects on socioemotional development observed for atazanavir regimen at 1-year observed in the Pediatric HIV/AIDS Cohort Study in the US.

- Implementing the WHO "Option B+" guidelines to ensure women initiate ART as soon as HIV infection is detected and prior to conception remains ideal.

Acknowledgements

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Arvin Saleh

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Early Career Awards

Extra slides

Maternal characteristics did between the eligible cohort and at cohort that completed follow-up

Characteristics	Participants with livebirths (n = 2167)	Mother-child dyad at 3-6 years follow-up (n = 667)
Maternal age (years)		
18-24	344 (15.9)	71 (10.6)
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Timing of antiretroviral therapy (cART) initiation	Participants with livebirths (n = 2167)	Mother-child dyad at 3-6 years follow-up (n = 667)
Timing of cART initiation		
Preconception	895 (41.3)	322 (48.3)
During pregnancy	1272 (58.7)	345 (51.7)
Trimester of cART initiation		
First (≤13 weeks)	214 (9.88)	63 (9.45)
Second (>13 weeks)	1058 (48.8)	282 (42.3)
Initiation before or after 20 weeks		
<20 weeks	883 (40.8)	240 (36.0)
≥20 weeks	389 (18.0)	105 (15.7)

Table 1. Core IDELA Domains and Skills

Gross and Fine Motor Development	Emergent Literacy and Language	Emergent Numeracy	Socio-emotional Development
Hopping on one foot	Print awareness	Measurement and comparison	Peer relations
Copying a shape	Expressive vocabulary	Classification/Sorting	Emotional awareness
Drawing a human figure	Letter identification	Number identification	Empathy
Folding Paper	Emergent writing	Shape identification	Conflict resolution
	Initial sound discrimination	One-to-one correspondence	Self-awareness
	Listening comprehension	Simple operations	
Simple problem solving			
Approaches to Learning: Persistence, motivation and engagement			