

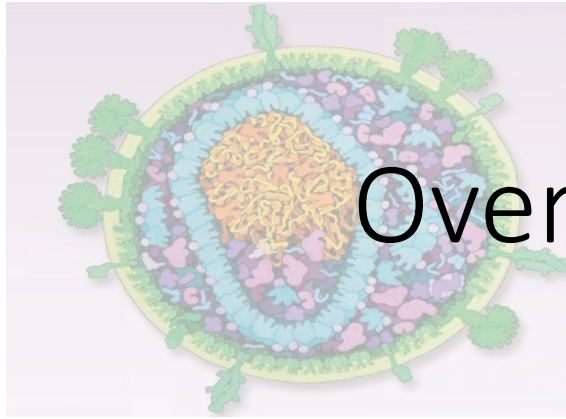
# The Evolving Epidemiology of HIV Exposed Uninfected Children

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# Overview

1. HEU children in global context
2. HEU child risk factors
3. HEU child outcomes – Current evidence
4. The long-term view

# Terminology

~~Mother to Child Transmission~~

Peri- and post-natal HIV transmission

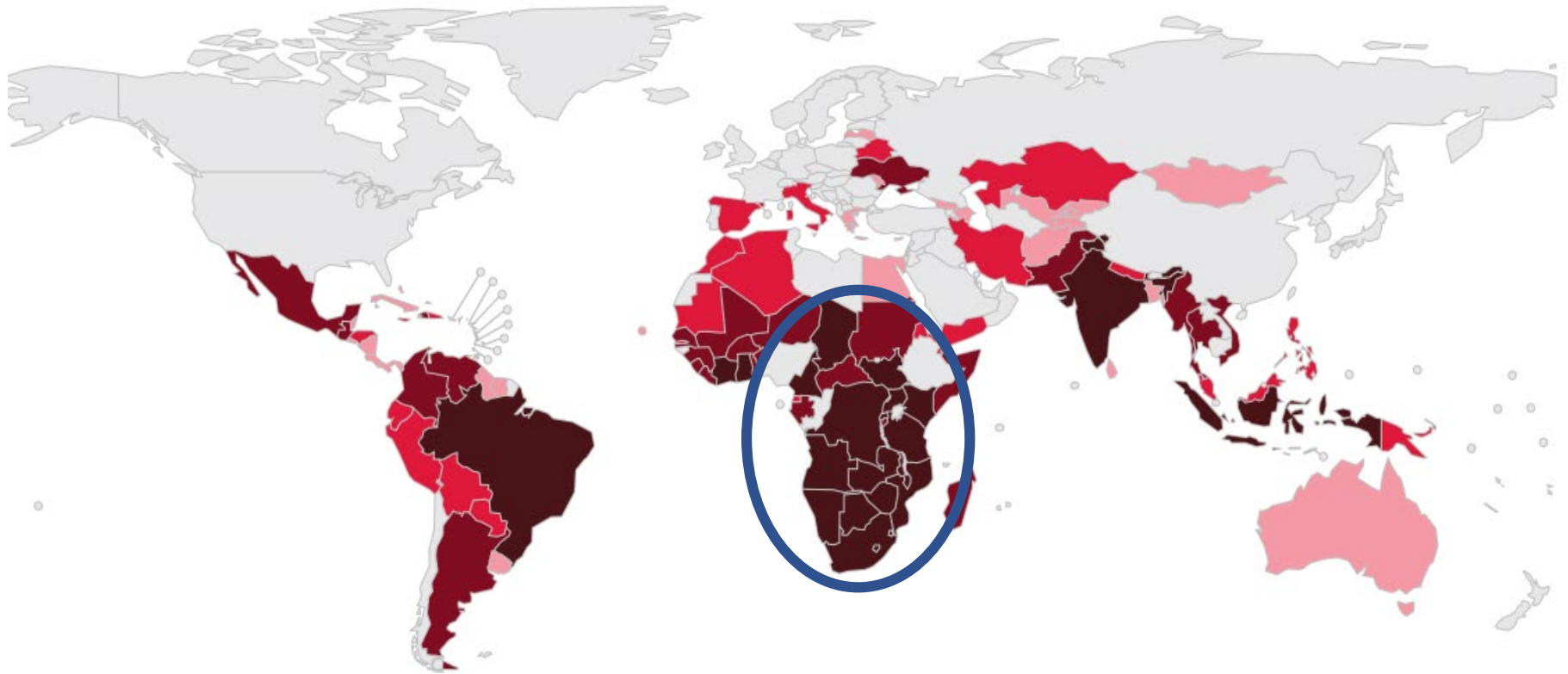
HIV exposed uninfected (HEU) = HIV affected



# Content Overview

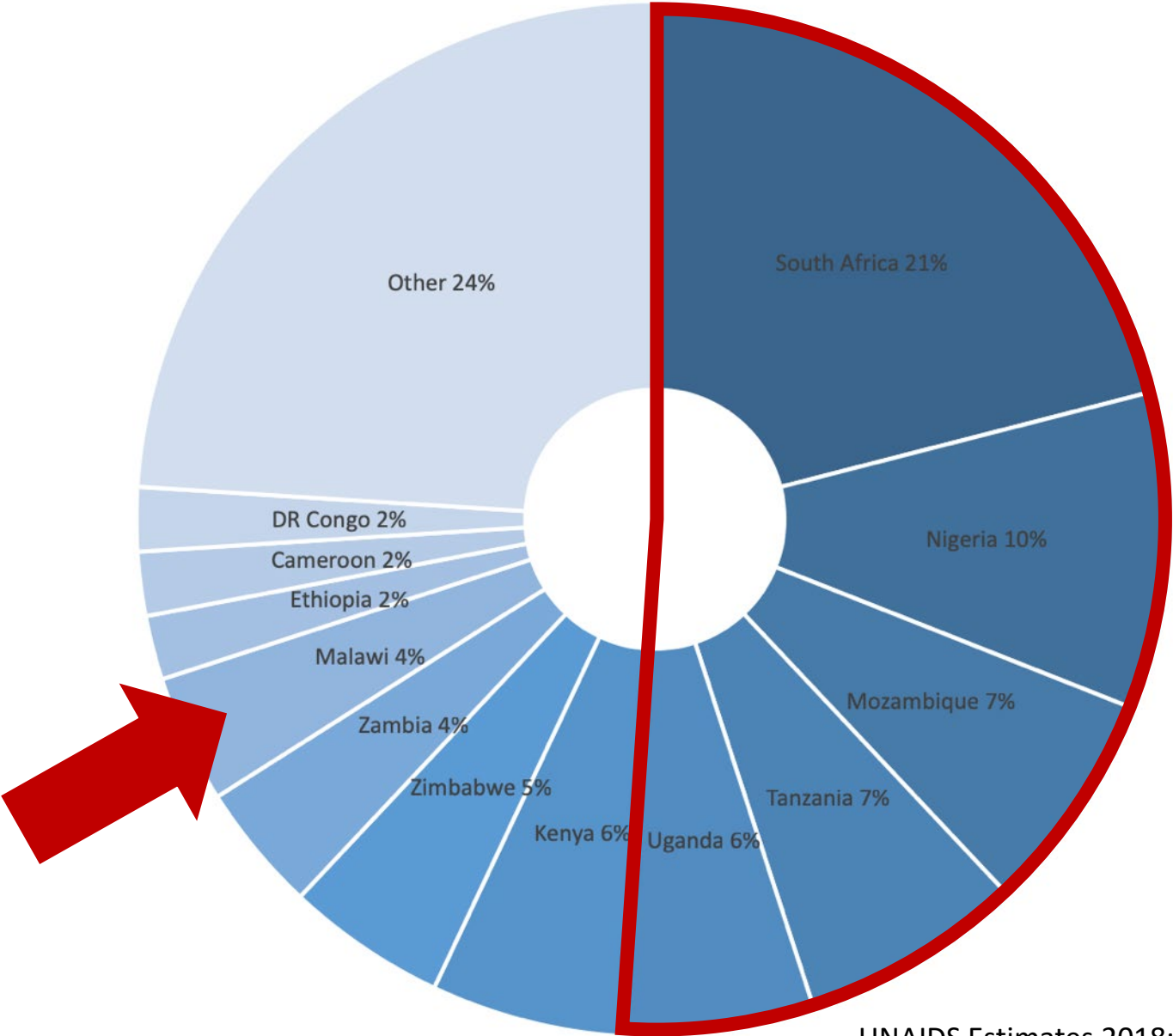
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# Africa in the Global HIV Epidemic

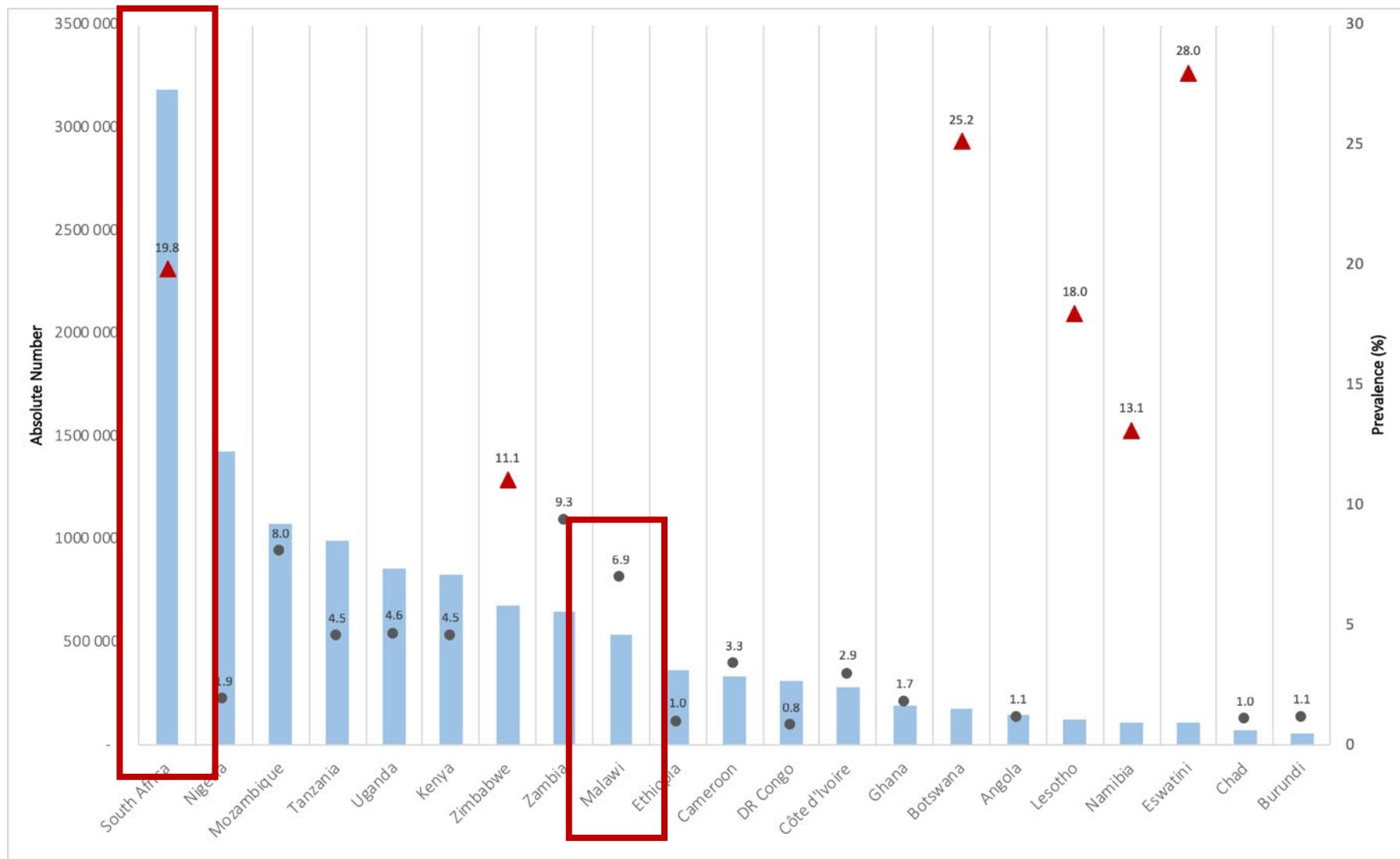


In 2017 14.8 million HEU children (age 0-14 years)  
- 90% in sub-Saharan Africa

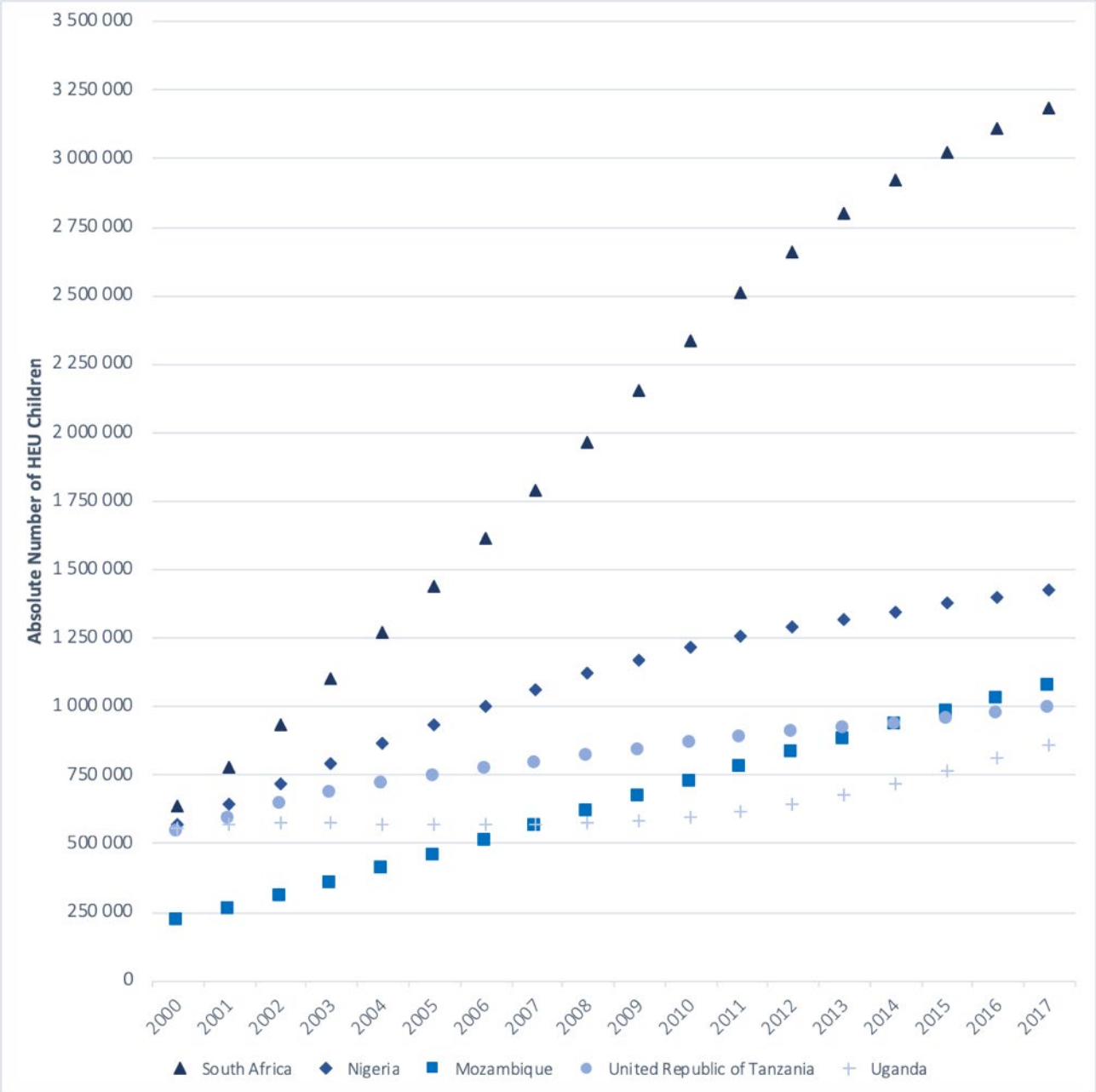
# Contributions by Country to Global HEU Child Burden in 2017



# Number and prevalence of HEU Children (0-14 years) in sub-Saharan African Focus Countries: 2017



# Increase in HEU Child Population Size:2000 -2017





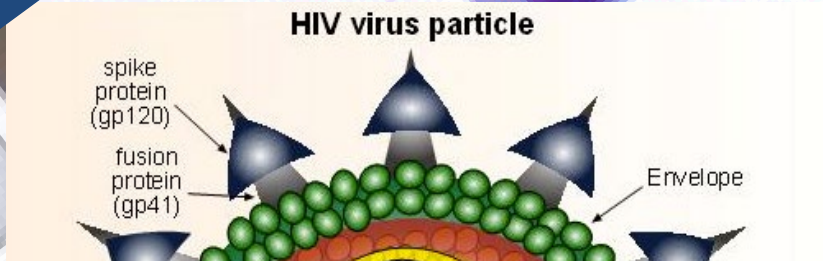


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## Universal Risk Factors



## Unique HEU Infant Risk Factors



# Variations in HIV and ARV Exposure Status

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HIV Exposure

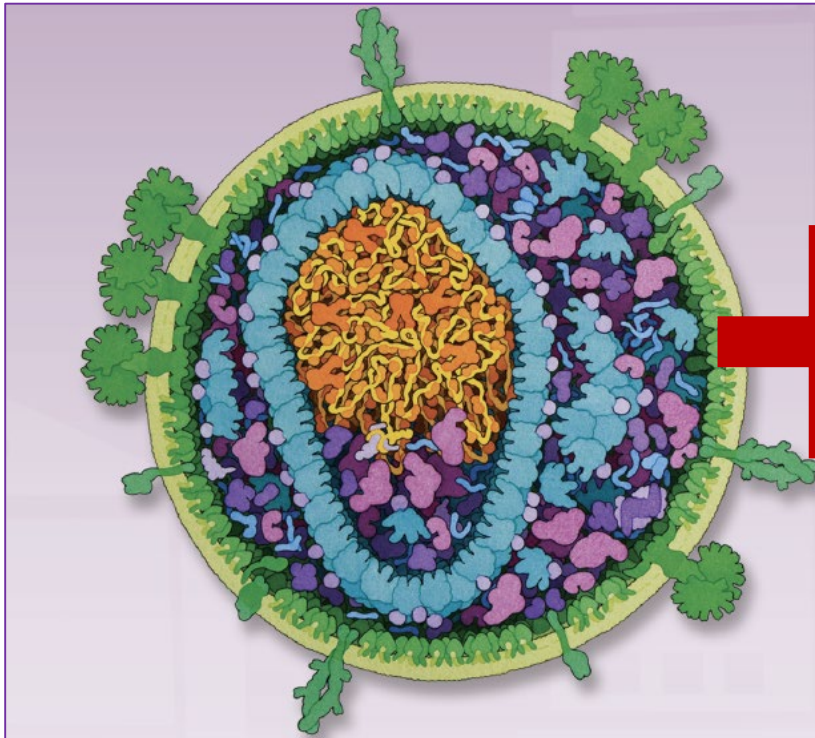
Varied timing  
and intensity

Antiretroviral Exposure

Varied timing  
and type

7% of all children in Malawi are  
exposed *in utero* to

A chronic viral infection  
HIV



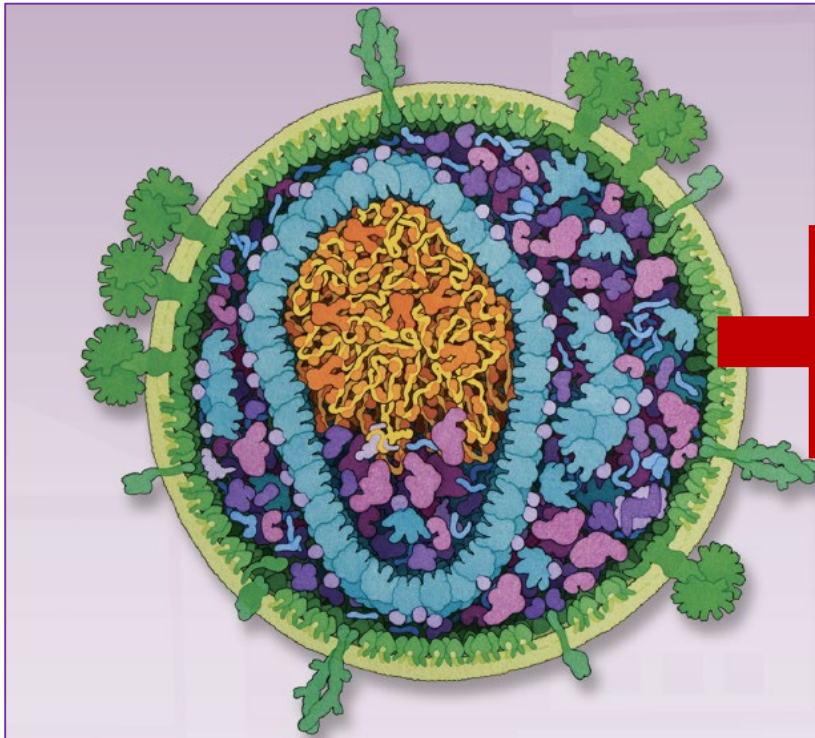
At least 3 highly active drugs  
Antiretroviral Therapy





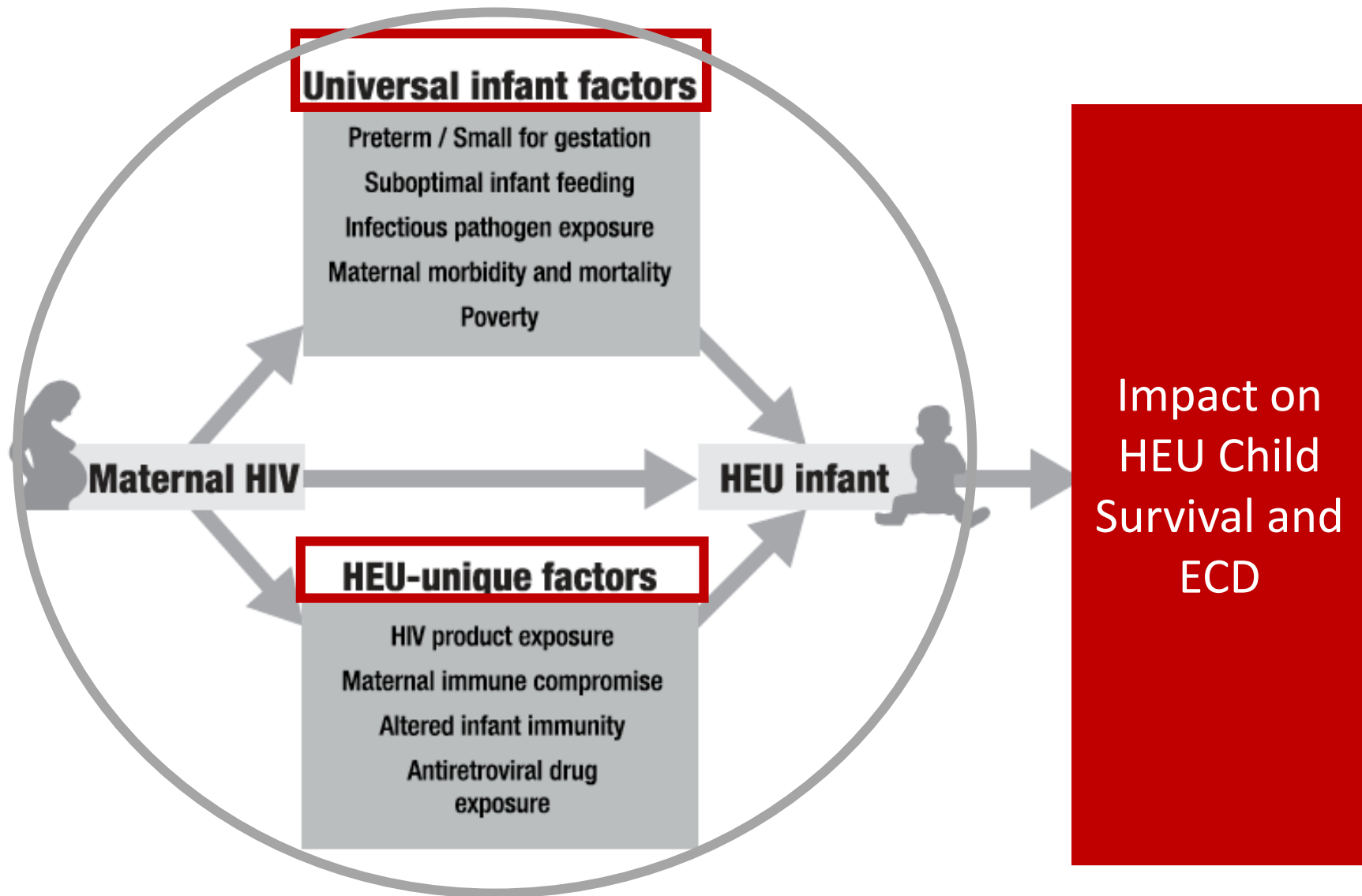
At least 1 in 5 children in  
Botswana, Eswatini, South Africa  
are exposed *in utero* to

A chronic viral infection  
HIV



At least 3 highly active drugs  
Antiretroviral Therapy







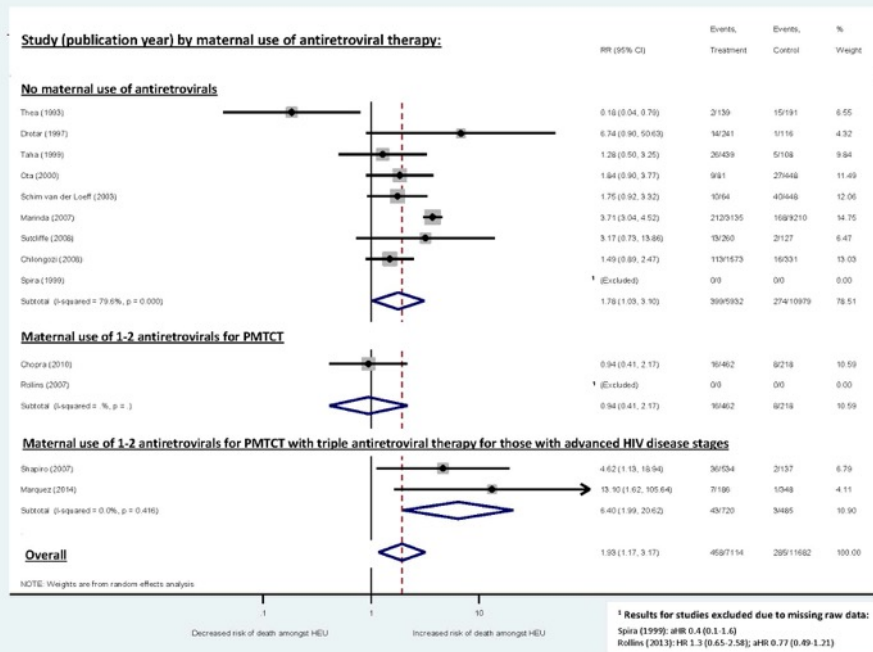
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# Elevated mortality in HEU children

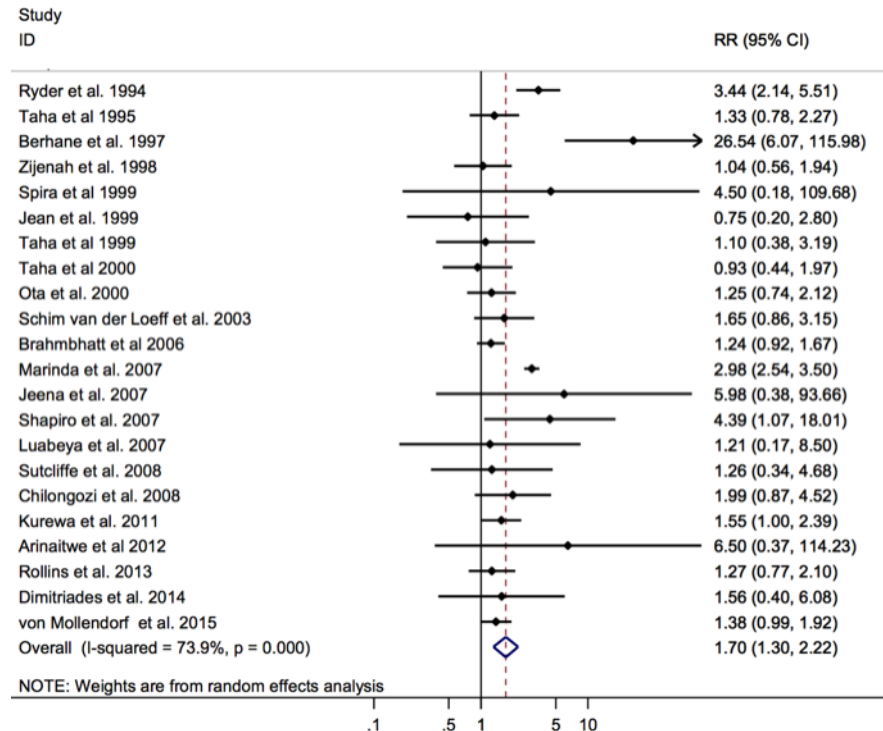
## Le Roux, TMIH 2016

Figure 2. Forest plot of mortality among HIV-exposed uninfected children compared to HIV-unexposed children, by maternal antiretroviral use



Overall: RR 1.93 (1.17; 3.17)

## Brennan, AIDS 2016



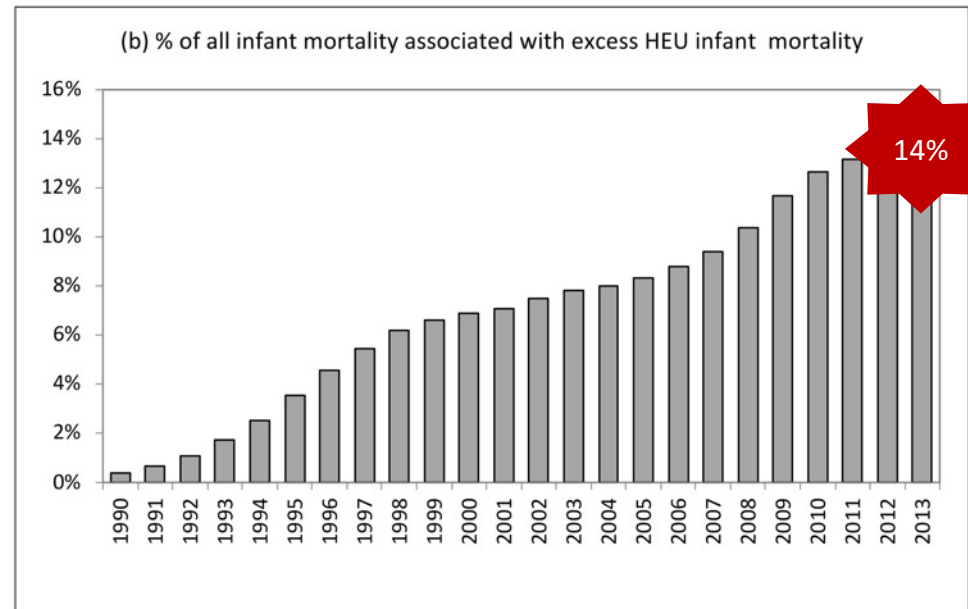
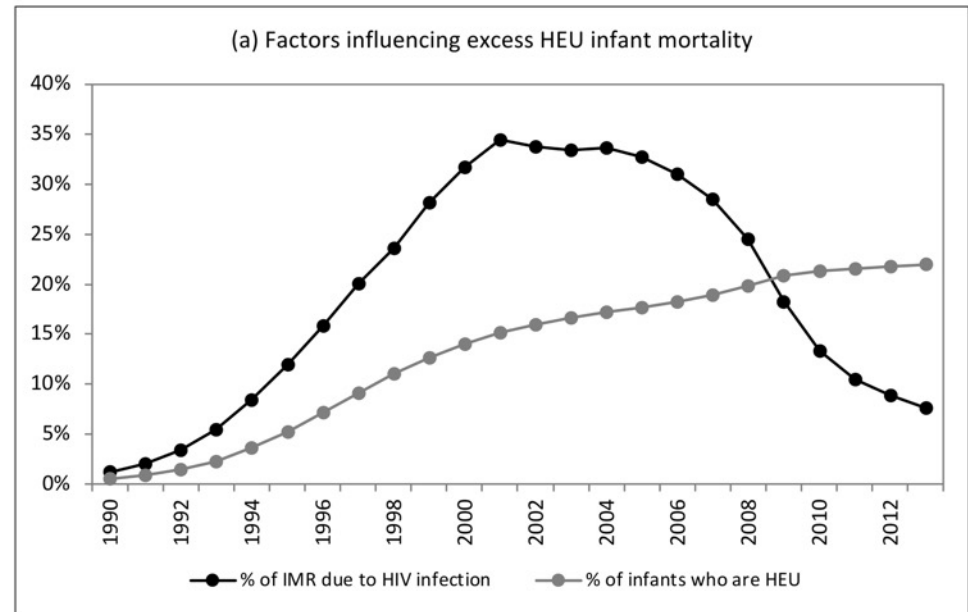
Overall: RR 1.70 (1.30; 2.22)

No change in this mortality trend with expanding maternal ART, improved maternal health and safer breastfeeding



# Population-level Effect of Excess Mortality in HEU Infants

- 2013 in Botswana and South Africa – 15% of all HIV-uninfected infant mortality associated with **excess mortality in HEU infants**
- In South Africa, mortality in children with HIV accounted for  $\pm 7\%$  of all childhood mortality, whereas **excess mortality in HEU infants** accounts for  $\pm 14\%$  of all infant mortality



# Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study



*Rebecca Zash, Denise L Jacobson, Modiegi Diseko, Gloria Mayondi, Mompoti Mmalane, Max Essex, Tendani Gaolethe, Chipo Petlo, Shahin Lockman, Lewis B Holmes, Joseph Makhema, Roger L Shapiro*



Lancet Global Health 2018; 6:e804-810

Tsepamo – an observational study in Botswana that captures birth outcomes of all births at 8 government health facilities -  $\pm 45\%$  of all births in Botswana; ongoing since 2014

Increased risk in **women with HIV on EFV-based ART** compared to **women without HIV** of:

Preterm birth (aRR 1.18; 95% CI 1.12,1.25)

Small for gestational age (aRR 1.30; 95% CI 1.23,1.38)

# HIV and Adverse Birth Outcomes

Women living with HIV in LMIC:  
40% increased risk of preterm birth when  
conceiving on ART compared to initiating  
ART during pregnancy  
(RR 1.41; 95% CI 1.22-1.63)

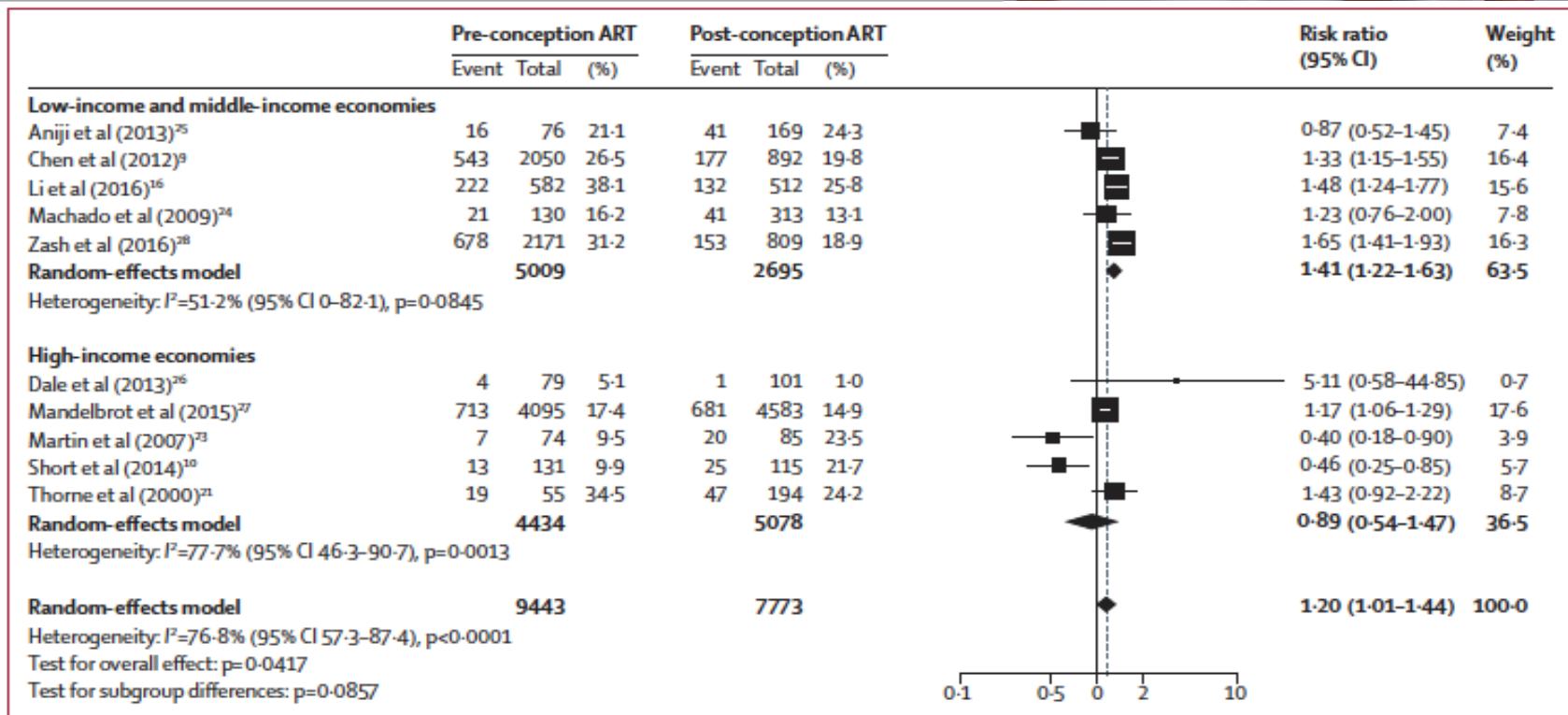
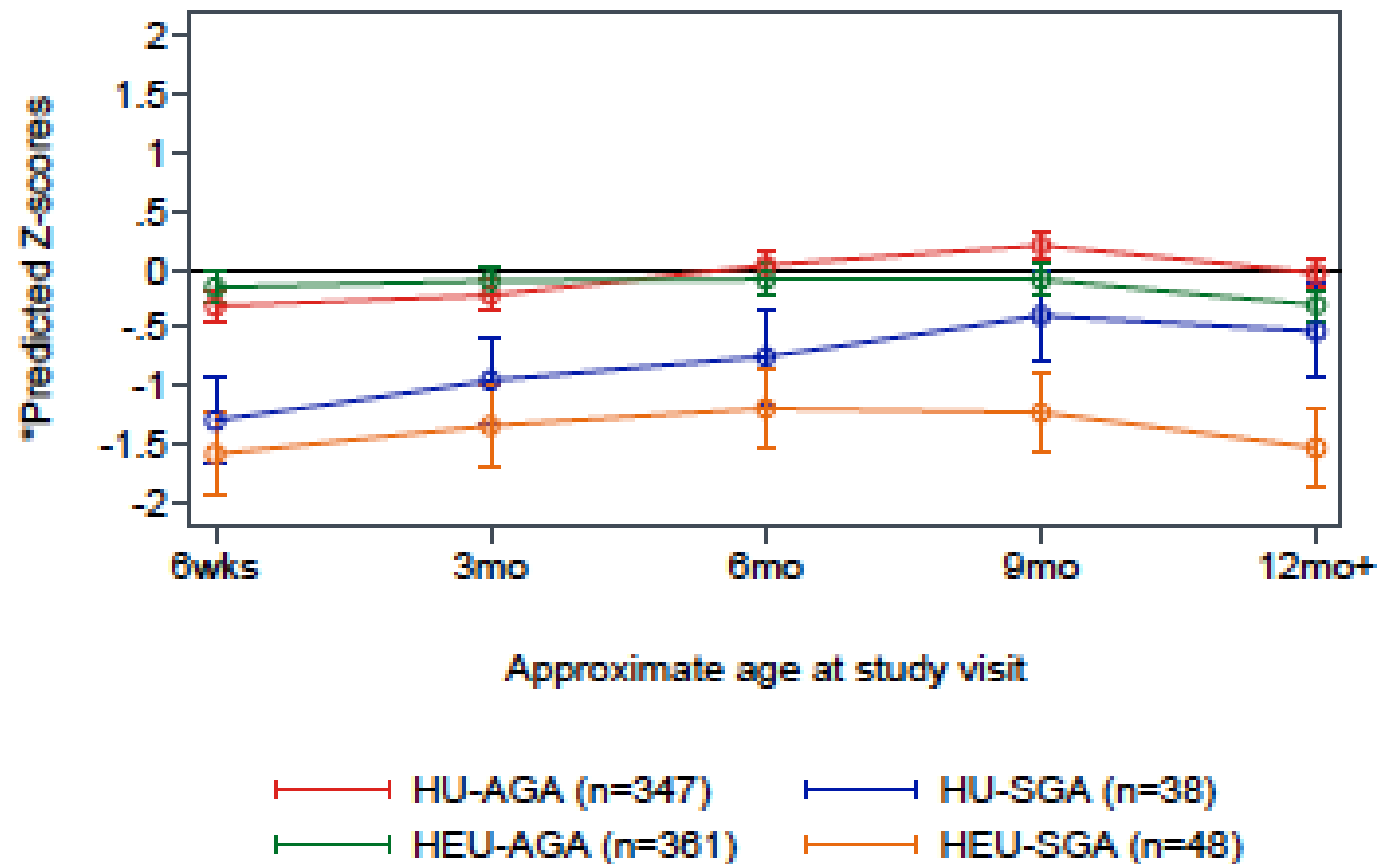


Figure 2: Forest plot of risk of preterm birth before 37 weeks (prematurity) in women with HIV who initiated ART before conception versus women who initiated ART after conception

# In utero HIV and ARV exposure – a fetal origin of disease

Length-for-age Z-scores from 6 weeks to 12 months of age





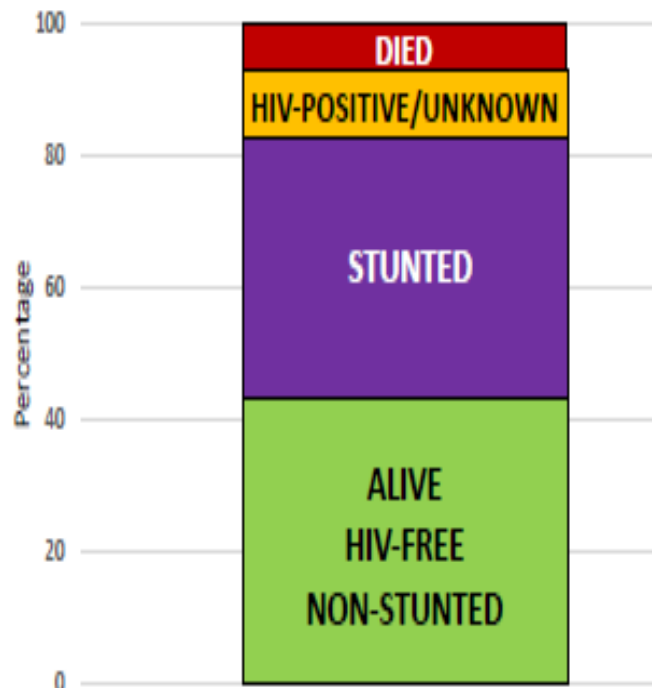
**SHINE**

Finding what helps children shine

# Sanitation Hygiene Infant Nutrition Efficacy

- HEU versus HUU at 18-months
  - Mortality RR 1.39 (95% CI 1.02, 1.89)
  - Stunting RR 1.48 (95% CI 1.34, 1.64)
- Significant differences in gross and fine motor, and language but not social or behavioral performance at 24-months
  - Combined nutrition + WASH interventions normalized HEU child neurodevelopment

**HEU Child Outcomes at 18 months**



Initiation of ART before pregnancy may reduce infectious morbidity risk in HEU infants

In Belgium,  
**conception on ART** was protective against  
immune abnormalities and  
infectious morbidity in HEU infants

What about in Southern Africa?



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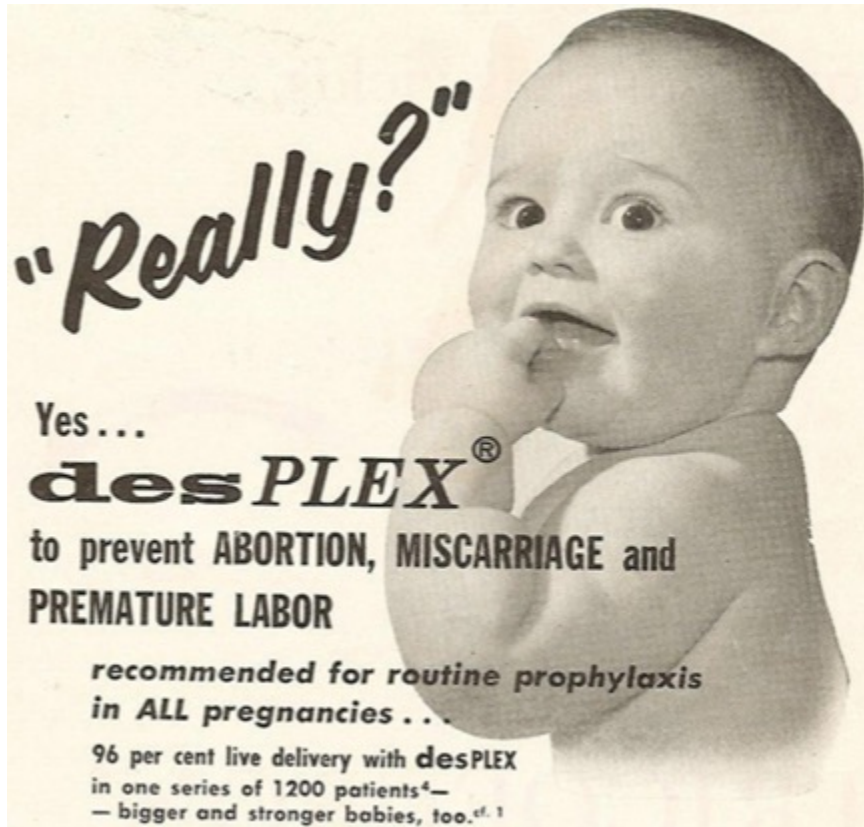
# Maternal and Child Health



## Maternal and Grandchild Health...



# Diethylstilbestrol (DES)

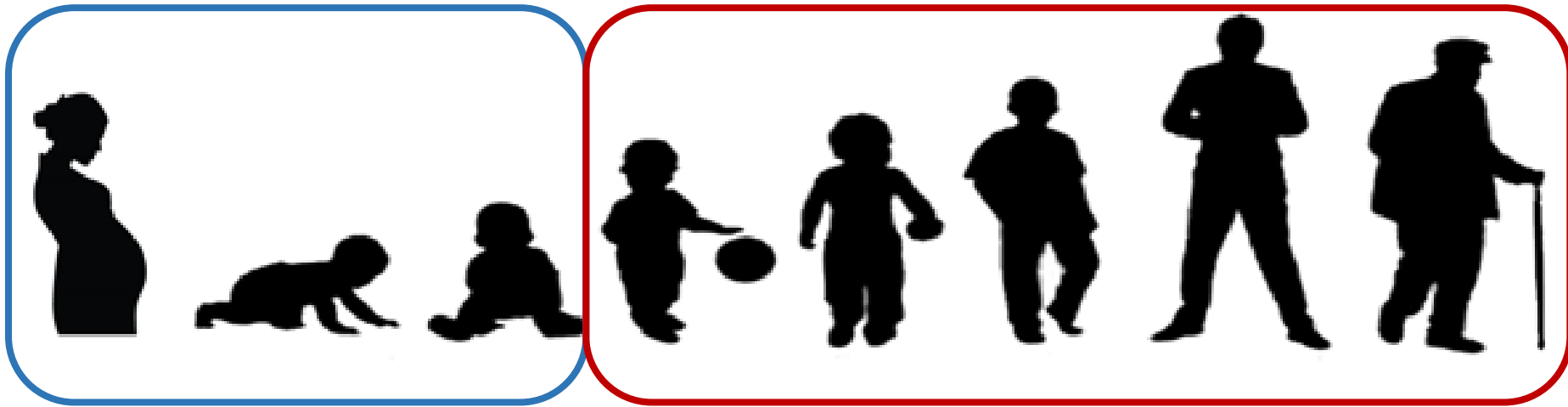


Advertisement for DES from a 1957 medical journal

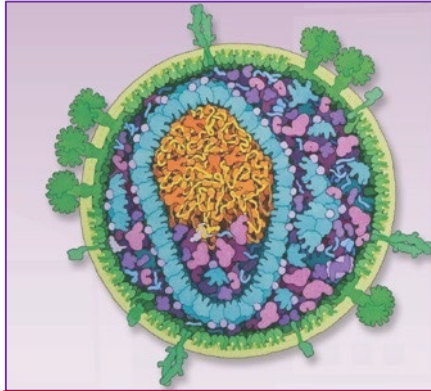
- 6 million in utero exposures 1940-1971
- Young adult women exposed *in utero*
  - 40 fold ↑ risk of rare cervical/vaginal cancers
  - 2 x ↑ risk of breast cancer
- Birth defects in offspring of DES Daughters - Epigenetic changes in primordial germ cells resulting in 2<sup>nd</sup> generation effects
- Also effects in sons and grandsons
- Effects of DES exposure **not recognized for decades (\*record of exposure)**

# Long Term View

## Surviving and Thriving throughout the Life Course

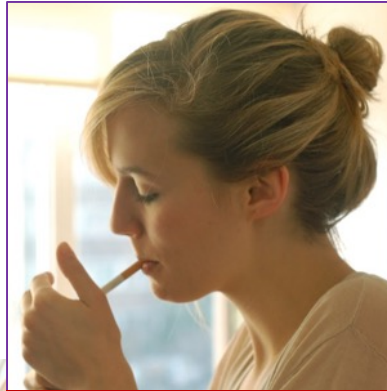
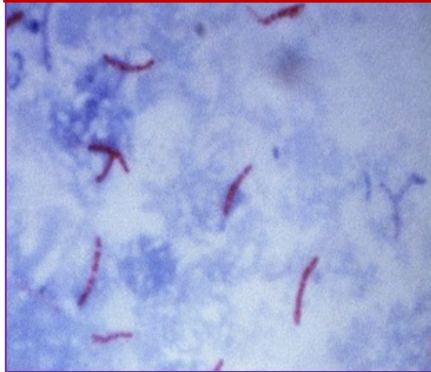


# Additive Exposures



HIV & ART

Tuberculosis &  
Treatment



Smoking



Alcohol



Obesity







# Finding the balance

Maternal Health

Child Health




# Finding the balance

Safety

Confidentiality







# The Evolving Epidemiology of HIV Exposed Uninfected Children

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# Mechanisms for Driving the HEU Child Outcomes Agenda

