# The Evolving Epidemiology of HIV Exposed Uninfected Children

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- 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

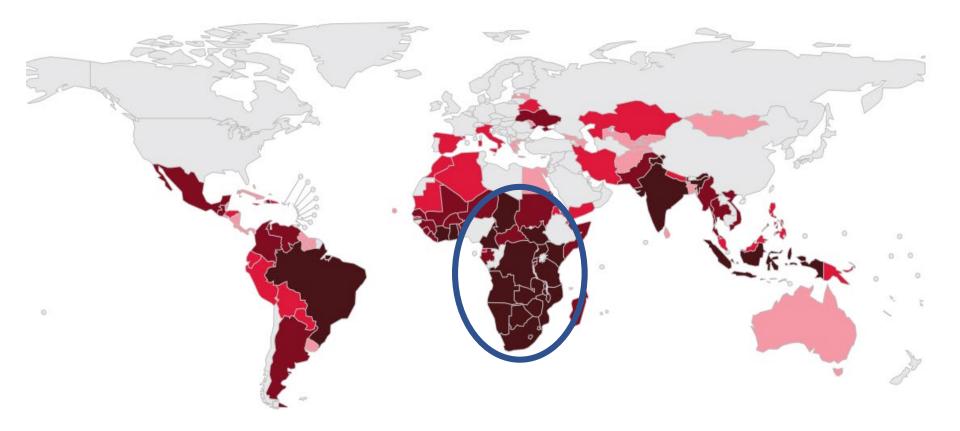
HIV exposed uninfected (HEU) = HIV affected



# 1. HEU children in global context

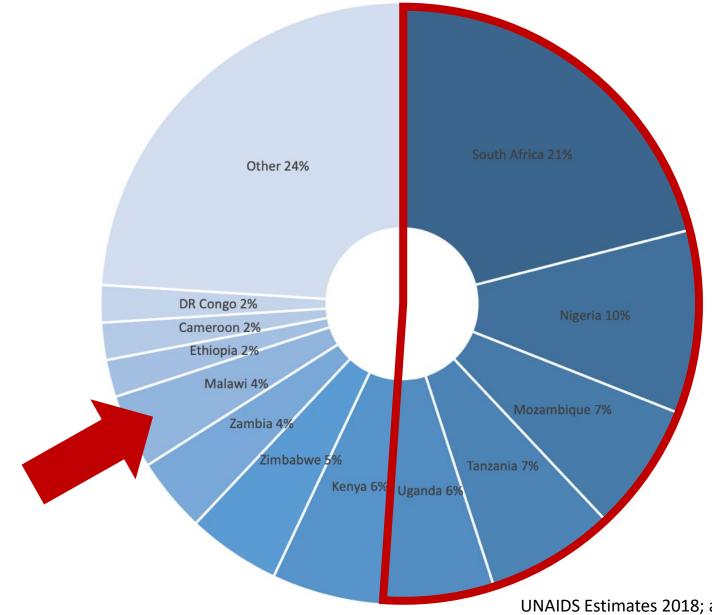
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# Africa in the Global HIV Epidemic



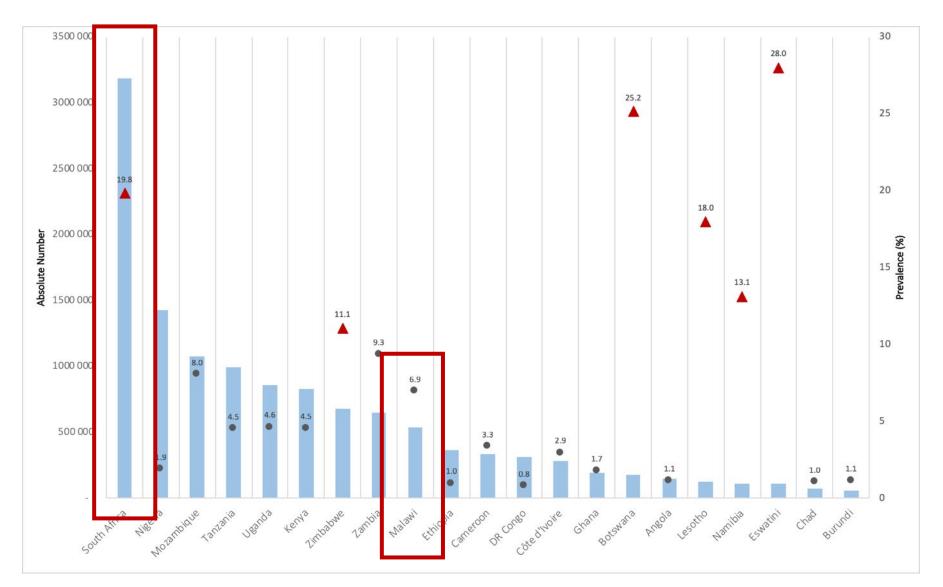
In 2017 14.8 million HEU children (age 0-14 years) - 90% in sub-Saharan Africa

# Contributions by Country to Global HEU Child Burden in 2017



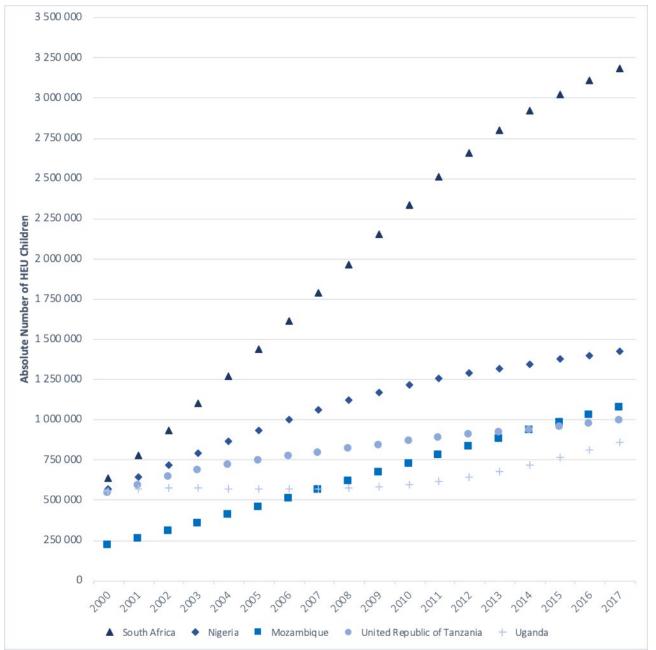
#### UNAIDS Estimates 2018; aidsinfo.unaids.org

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



UNAIDS Estimates 2018; aidsinfo.unaids.org

# Increase in HEU Child Population Size:2000 -2017



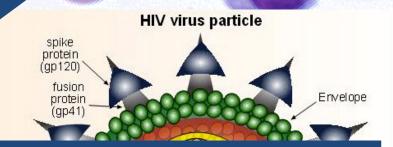


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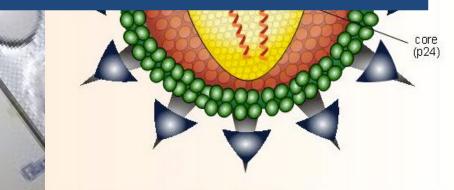


### <u>Universal</u> Risk Factors

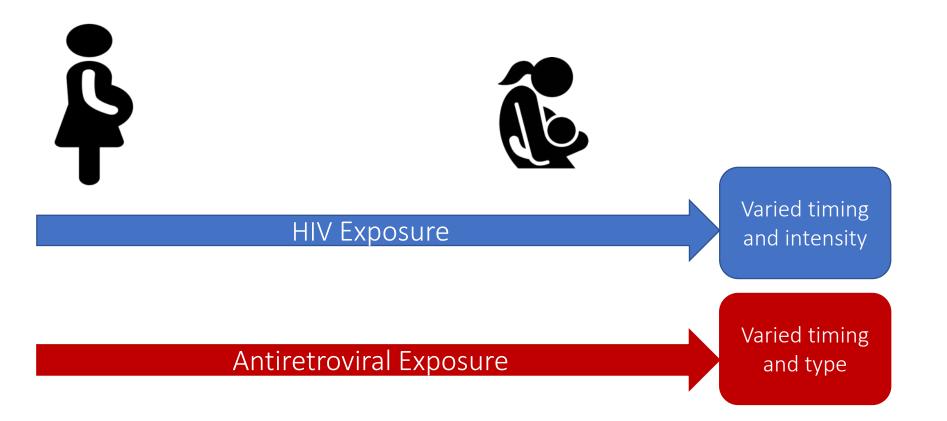
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## **Unique** HEU Infant Risk Factors



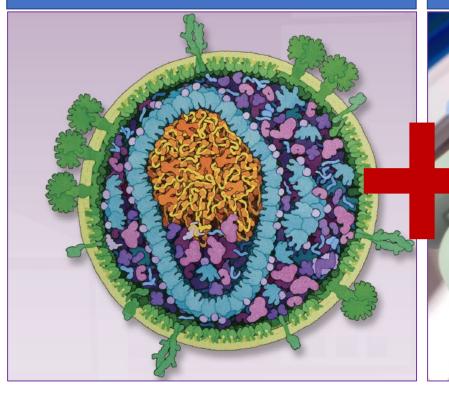
# Variations in HIV and ARV Exposure Status



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



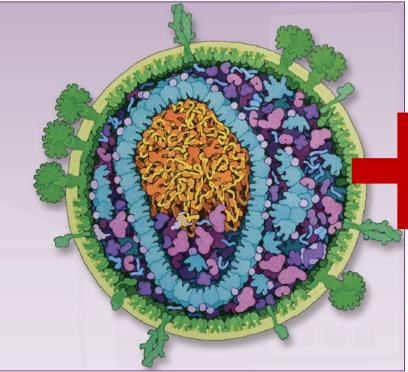
### At least 3 highly <u>active drugs</u> Antiretroviral Therapy



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

### A chronic <u>viral infection</u> HIV

### At least 3 highly <u>active drugs</u> Antiretroviral Therapy





### Universal infant factors

Preterm / Small for gestation Suboptimal infant feeding Infectious pathogen exposure Maternal morbidity and mortality Poverty

Maternal HIV

### **HEU** infant

### **HEU-unique factors**

HIV product exposure Maternal immune compromise Altered infant immunity Antiretroviral drug exposure Impact on HEU Child Survival and ECD

Slogrove, Frigati, Gray, 2016



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# Elevated mortality in HEU children

Study

ID

### Le Roux, TMIH 2016

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

### Brennan, AIDS 2016

tudy (publication year) by maternal use of antiretroviral therapy:		Events,	Events,	*
	RR (95% CI)	Treatment	Control	Weight
o maternal use of antiretrovirals				
ea (1903)	0.18(0.04, 0.79)	2/139	15/191	6.55
tar (1997)	6.74 (0.90, 50.63)	14/241	1/116	4.92
a (1999)	1.28 (0.50, 3.25)	26/439	5/108	9.84
(2000)	1.84 (0.90, 3.77)	9/81	271448	11.49
im van der Loeff (2003)	1.76 (0.92, 3.32)	10/64	40/448	12.06
rinda (2007)	3.71 (3.04, 4.52)	212/3135	168/9210	14.75
cliffe (2008)	3.17 (0.73, 13.86)	13/260	2/127	6.47
longozi (2008)	1.49 (0.89, 2.47)	113/1573	16/331	13.03
ra (1990)	<ul> <li>(Excluded)</li> </ul>	0/0	0/0	0.00
total (I-squared = 79.6%, p = 0.000)	1.76 (1.09, 3.10)	399/5932	274/10979	78.51
aternal use of 1-2 antiretrovirals for PMTCT				
pra (2010)	0.94 (0.41, 2.17)	16/462	8/218	10.59
ins (2007)	<ul> <li>(Excluded)</li> </ul>	0/0	010	0.00
tot# (l-quared= %, p = .)	0.94(0.41, 2.17)	16/462	8/218	10.59
faternal use of 1-2 antiretrovirals for PMTCT with triple antiretroviral therapy for the	se with advanced HIV disease	stages		
piro (2007)	4.62 (1.13, 18.94)	36/534	2/137	6.79
guez (2014)	13.10 (1.62, 105.64)	7/186	1048	4.11
xtotal (i-squared = 0.0%, p = 0.416)	6.40 (1.99, 20.62)	43/720	3/485	10.90
Iverall 🔷	1.93 (1.17, 3.17)	458/7114	295/11682	100.00
TE: Weights are from random effects analysis				
.1 1 10	<sup>1</sup> Results for stu	dies excluded d	ue to missing	raw data
Decreased risk of death amongst HEU Increased risk of death amon			in the second	

#### Ryder et al. 1994 Taha et al 1995 Berhane et al. 1997

Zijenah et al. 1998		-	+ i			1.04 (0.56, 1.94)
Spira et al 1999			- i	-		4.50 (0.18, 109.68)
Jean et al. 1999	_		Η÷	-		0.75 (0.20, 2.80)
Taha et al 1999		_	+ i	_		1.10 (0.38, 3.19)
Taha et al 2000		_	++			0.93 (0.44, 1.97)
Ota et al. 2000			+++			1.25 (0.74, 2.12)
Schim van der Loeff et al. 2003			++	_		1.65 (0.86, 3.15)
Brahmbhatt et al 2006			+			1.24 (0.92, 1.67)
Marinda et al. 2007				+		2.98 (2.54, 3.50)
Jeena et al. 2007			++			5.98 (0.38, 93.66)
Shapiro et al. 2007			+	-		4.39 (1.07, 18.01)
Luabeya et al. 2007			++		-	1.21 (0.17, 8.50)
Sutcliffe et al. 2008			- <b>+•</b> +			1.26 (0.34, 4.68)
Chilongozi et al. 2008			+++			1.99 (0.87, 4.52)
Kurewa et al. 2011			+			1.55 (1.00, 2.39)
Arinaitwe et al 2012			++			6.50 (0.37, 114.23)
Rollins et al. 2013			<b>→•</b> +			1.27 (0.77, 2.10)
Dimitriades et al. 2014			++			1.56 (0.40, 6.08)
von Mollendorf et al. 2015			<b>+</b>			1.38 (0.99, 1.92)
Overall (I-squared = 73.9%, p = 0.000)						1.70 (1.30, 2.22)
NOTE: Weights are from random effects and	lucie					
NOTE: Weights are from random effects ana	lysis		<u> </u>			
	.1	.5	1	5	10	

RR (95% CI)

3.44 (2.14, 5.51)

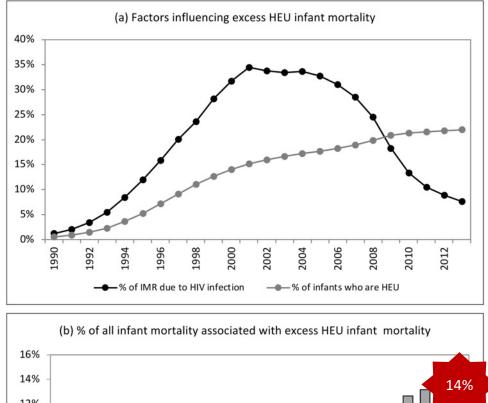
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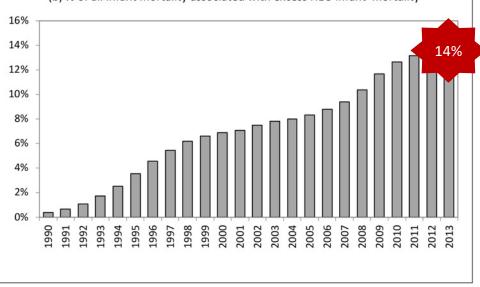
## Overall: RR 1.70 (1.30; 2.22)

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 ±7% of all childhood mortality, whereas excess mortality in HEU infants accounts for ± 14% of all infant mortality





Slogrove, Johnson, Powis, JTP 2018

#### From Thembisa Demographic Model

### Comparative safety of dolutegravir-based or efavirenz-based *W* (1) antiretroviral treatment started during pregnancy in Botswana: an observational study

Rebecca Zash, Denise L Jacobson, Modiegi Diseko, Gloria Mayondi, Mompati 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 - ±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

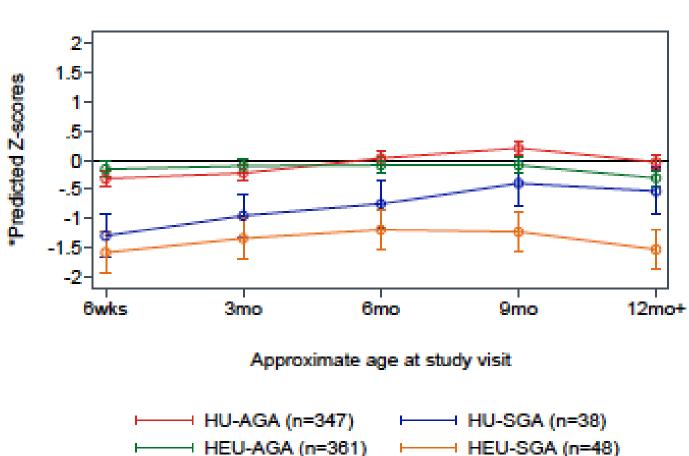
Women living with HIV in LMIC: 40% increased risk of preterm birth when conceiving on ART compared to initiating ART during pregnancy (RR 1.41; 95% CI 1.22-1.63)



	Pre-co	Pre-conception ART			oncept	ionART			Risk ratio	Weight	
	Event	Total	(%)	Event	Total	(%)				(95% CI)	(%)
Low-income and middle-income econom	nies										
Aniji et al (2013) <sup>75</sup>	16	76	21.1	41	169	24.3				0-87 (0-52-1-45)	7.4
Chen et al (2012)9	543	2050	26.5	177	892	19-8				1.33 (1.15-1.55)	16.4
Li et al (2016) <sup>16</sup>	222	582	38.1	132	512	25-8				1.48 (1.24-1.77)	15-6
Machado et al (2009) <sup>24</sup>	21	130	16-2	41	313	13-1		-		1.23 (0.76-2.00)	7-8
Zash et al (2016) <sup>28</sup>	678	2171	31.2	153	809	18-9				1.65 (1.41-1.93)	16-3
Random-effects model		5009			2695			•		1.41 (1.22-1.63)	63.5
Heterogeneity: l <sup>2</sup> =51·2% (95% Cl 0-82·1), p	=0-0845										
High-income economies											
Dale et al (2013) <sup>26</sup>	4	79	5.1	1	101	1-0				<ul> <li>5-11 (0-58–44-85)</li> </ul>	0-7
Mandelbrot et al (2015) <sup>27</sup>	713	4095	17.4	681	4583	14.9				1.17 (1.06-1.29)	17-6
Martin et al (2007) <sup>23</sup>	7	74	9.5	20	85	23·5		<b>⊢</b> – i		0.40 (0.18-0.90)	3-9
Short et al (2014) <sup>10</sup>	13	131	9.9	25	115	21.7		■ :		0.46 (0.25-0.85)	5.7
Thorne et al (2000) <sup>21</sup>	19	55	34.5	47	194	24.2		┼╪═╾╴		1.43 (0.92-2.22)	8-7
Random-effects model		4434			5078			-		0.89 (0.54-1.47)	36.5
Heterogeneity: I <sup>2</sup> =77·7% (95% Cl 46·3-90·)	7), p=0-0013										
Random-effects model		9443			7773			•		1.20 (1.01-1.44)	100-0
Heterogeneity: 12=76-8% (95% CI 57-3-87-4	4), p<0·0001	L									
Test for overall effect: p=0.0417											
Test for subgroup differences: p=0.0857							0.1 0	5 0 2	10		

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 Uthman, Lancet HIV 2016

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



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

"Adjusted mixed effects model; time-interaction p=0.08

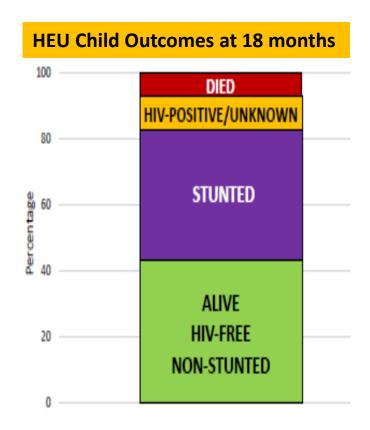
Stanzi Le Roux – Lancet Child & Adolescent Health 2019

# Sanitation Hygiene Finding what helps children shine Infant Nutrition Efficacy

HEU versus HUU at 18-months

SHINE

- 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



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...

# Diethylstilbesterol (DES)

Yes... desPLEX

"Really

to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

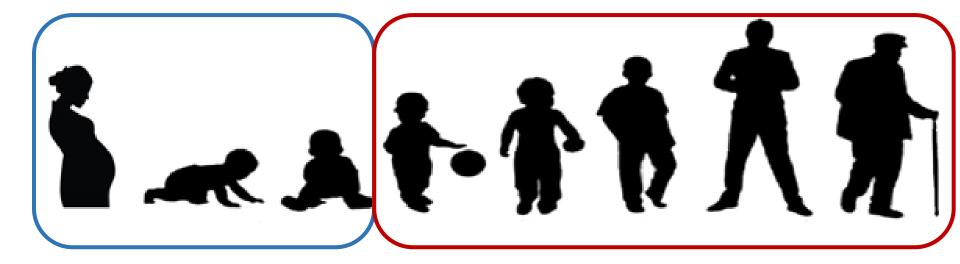
recommended for routine prophylaxis in ALL pregnancies...

96 per cent live delivery with desPLEX in one series of 1200 patients<sup>4</sup>— — bigger and stronger babies, too.<sup>et. 1</sup>

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
  - $2 \times \uparrow$  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





# Finding the balance



# Finding the balance



# The Evolving Epidemiology of HIV Exposed Uninfected Children

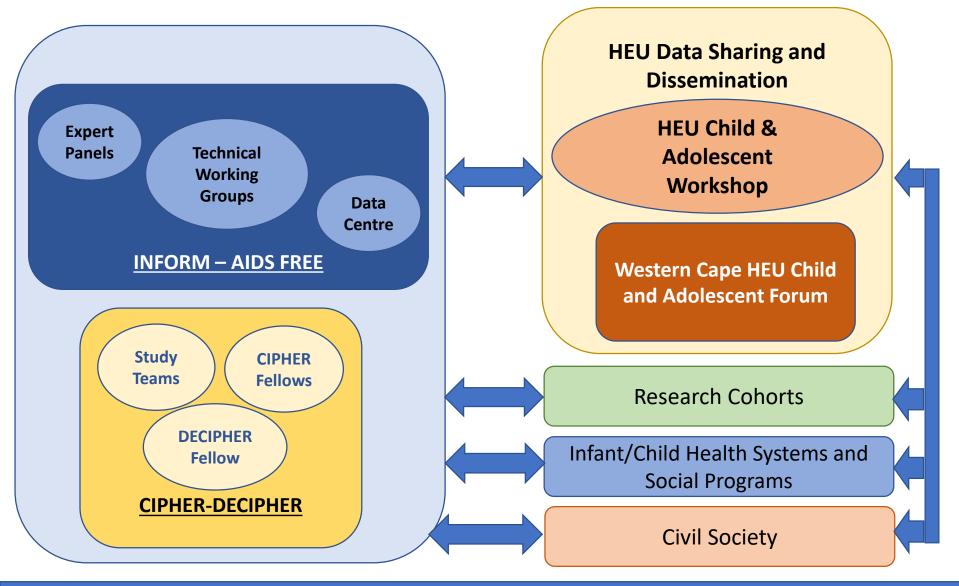
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### **Mechanisms for Driving the HEU Child Outcomes Agenda**



CIPHER World Health Organization UNICEF

Ministries of Health/Departments of Health