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BHIVA ‘Best of CROI’ feedback webinars 2024

Pregnancy and Paediatric Update

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Nottingham University Hospitals Trust

This educational event is supported by

GILEAD Creating Possible
MSD
ViiV Healthcare

With thanks to those presenting research for permission to use slides for ‘Best of CROI’

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Conflict of Interest

I have received conference sponsorship and participated in advisory boards for Gilead Sciences and ViiV Healthcare

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Pregnancy

- Safety of antiretrovirals in pregnancy

00933

Birth Outcomes Following Bictegravir Use During Pregnancy

Rosemary Olivero[1], Paige Williams[2], George Sawyer[2], Lynn Yee[3], Kunjal Patel[2], Sonia Hernandez-Diaz[2], Kathleen Powis[2], Mary Paul[4], Ellen G. Chadwick[3] the Pediatrics HIV/AIDS Cohort Study (PHACS)

[1]Helen DeVos Children's Hospital of Corewell Health, Grand Rapids, MI, USA, [2]Harvard University, Boston, MA, USA, [3]Northwestern University, Chicago, IL, USA, [4]Baylor College of Medicine, Houston, TX, USA

Table 2: Birth Outcomes of Infants Exposed to ≥ 7 Days of Bictegravir during Gestation

Infant Outcome	Pre-Conception Initiation (N=76)	Post-Conception Initiation (N=68)	Total (N=144)
Gestational age	N=76* 37.9 (1.5)	N=67* 38.4 (1.4)	N=143* 38.2 (1.5)
Preterm birth	15/76, 19.7% (11.5%, 30.5%)	5/67*, 7.5% (2.5%, 16.6%)	20/143*, 14.0% (8.8%, 20.8%)
Small for gestational age	3/76*, 3.9% (0.8%, 11.1%)	12/66*, 18.2% (9.8%, 29.6%)	15/142*, 10.6% (6.0%, 16.8%)
Congenital anomalies (among pregnancies with 1st trimester bictegravir exposure)**	4/76, 5.3% (1.5%, 12.9%)	1/23, 4.3% (0.1%, 21.9%)	5/99, 5.1% (1.7%, 11.4%)
Birth weight Z-Score (adjusted for gestational age)	N=76* -0.50 (0.84)	N=66* -0.47 (1.03)	N=142* -0.49 (0.93)
Birth length Z-Score (adjusted for gestational age)	N=53* 0.04 (1.08)	N=50* 0.12 (1.19)	N=103* 0.08 (1.13)

Data shown as % (with 95% CI) or mean (SD). *Differences between N in top row and column are due to incomplete data

**Anomalies included ventricular septal defect, Turner syndrome, Dandy-Walker malformation, polydactyly, and Jacob's syndrome

Equivalent to background

99 infants (69%) were exposed to BIC in the first trimester

In this US cohort, the use of ***bictegravir*** during pregnancy appears to be common. Findings ***do not suggest early safety signals*** for adverse birth outcomes with bictegravir use in pregnancy.

With thanks to Dr Charlotte Short

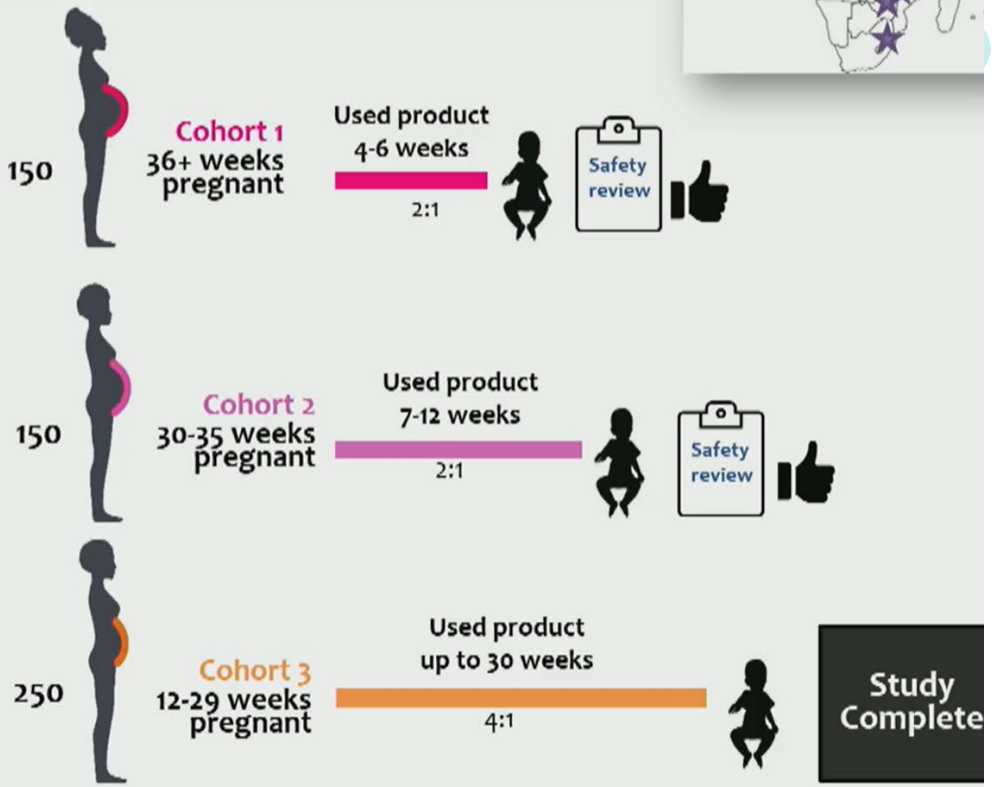
Safety of Dapivirine Vaginal Ring and Oral PrEP for HIV Prevention in the Second Trimester

Felix Mhlanga *University of Zimbabwe College of Health Sciences Clinical Trials Research Centre*

deliver

MTN-042 Study Design

- Key eligibility criteria: 18-40 years old, singleton pregnancy, ultrasound confirmed gestational age, no history of pregnancy complications
- Participants randomly assigned to use either the monthly DVR or daily TDF/FTC until delivery (or 41 6/7 weeks gestation)
  - 2:1 randomization for cohorts 1 and 2
  - 4:1 randomization for cohort 3
- Interim safety reviews conducted by an independent panel between cohorts
- Pregnancy outcomes and complications compared to local background rates (systematic chart review = 10,138 records MTN-042B)



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Pregnancy Complications

Pregnancy complication	DVR (n=200) n (%)	Oral PrEP (n=48) n (%)	Total (n=248) n (%)	Local background frequencies (95% CI) of pregnancy complications*
Any hypertensive disorder of pregnancy	19 (9%)	7 (14%)	26 (10%)	10.5% (10.0,11.3)
Gestational hypertension	15 (7%)	6 (12%)	21 (8%)	4.4% (4.0,4.8)
Pre-eclampsia without severe features	3 (1%)	0 (0%)	3 (1%)	2.2% (1.9,2.5)
Pre-eclampsia with severe features	1 (0.4%)	1 (2%)	2 (1%)	2.1% (1.9,2.4)
Eclampsia	0 (0%)	0 (0%)	0 (0%)	0.6% (0.5,0.8)
Peripartum/Antepartum hemorrhage	5 (3%)	0 (0%)	6 (2%)	--
Postpartum hemorrhage	3 (1%)	0 (0%)	3 (1%)	3.2% (2.9,3.6)

No infectious complications (puerperal sepsis, endometritis, chorioamnionitis) were observed

*Balkus et al. PLoS One 2021 Mar 31;16(3):e0248423

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Pregnancy Outcomes

Cohort 3 (enrolled at 12-29 weeks)	DVR (n=200) n (%)	Oral PrEP (n=48) n (%)	Total (n=248) n (%)	MTN 042B (n=10,426†) n (%)
Live births	197 (99)	48 (100)	245 (99)	9,767 (93.7)
Full term (≥ 37weeks)	189 (95)	45 (94)	234 (94)	8448 (81)
Premature (<37 weeks)	8 (4)	3 (6)	11 (4)	1319 (12.7)
Stillbirth/intrauterine fetal demise (>20 weeks)*	2 (1)	0	2 (1)	413 (4.0)
Spontaneous abortion (<20 weeks)	1 (1)	0	1 (<1)	-
Therapeutic/election abortion	0	0	0	-

*Not related to study product

†246 records pregnancy outcome not documented

MTN microbicide trials network

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Maternal and Infant Adverse Events

Adverse Events	Cohort 3 (12-29 weeks)		
	DVR N (%)	Oral PrEP N (%)	Total N (%)
Maternal Participants	202	49	251
Maternal participants with ≥1 composite AE[1]	24 (12)	4 (8)	28 (11)
Maternal Death	0	0	0
Maternal HIV seroconversion	0	0	0
Infant participants	196	48	244
Infant participants with ≥1 composite AE[1]	32 (16)	2 (4)	34 (14)
Congenital Anomalies	9 (5)	2 (4)	11 (4)
Infant Death	2 (1)	0	2 (0.8)

[1]Composite safety for both mother and infant encompassed all serious adverse events (SAEs) and grade 3 or higher adverse events (AEs) as per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events through 6 weeks postpartum

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Pregnancy

- Dolutegravir and hypertension in pregnancy

Association of HIV and Dolutegravir With Changes in Blood Pressure During Pregnancy and Postpartum

Jennifer Jao *Northwestern University, Chicago, IL, USA*

Methods

- Women in ORCHID recruited from community-based antenatal clinics in Cape Town, South Africa
  - Ages ≥ 16 years
  - <18 weeks gestation
  - All WLH received tenofovir + lamivudine + dolutegravir (TLD)
- Antenatal and postnatal follow-up through 6 weeks postpartum with serial, standardized BP measures
  - Three measures of the left arm using an automated, calibrated BP cuff sized to participant BMI conducted separate from routine care
- Cox proportional hazards models were fit to asses:

HIV and TLD use → **Incident HTN**
BP>140/90, or
Initiation of antihypertensive

***O**besogenic o**R**igins of maternal and **C**hild metabolic **H**ealth **I**nvolving **D**olutegravir (**ORCHID**)*

Table 1. Characteristics of participants at enrolment by HIV status

Characteristic	WLH (n = 797)	HIV -ve (n = 1097)	Total (n = 1894)
Age - years	30 [26 - 34]	26 [23 - 31]	28 [24, 32]
Gestational Age	13 [9 – 15]	12 [9 – 15]	13 [9 - 15]
Gestational Age less than or equal to 14 weeks	550 (69%)	796 (73%)	1,346 (71%)
Primigravida	158 (20%)	433 (39%)	591 (31%)
BMI - kg/m^2	29 [25 - 34]	30 [26 – 35]	30 [25 – 35]
BMI greater than or equal to 30 kg/m^2	362 (45%)	544 (50%)	906 (48%)
Current Smoker	60 (8%)	62 (6%)	122 (6.4%)
Mean Systolic Blood Pressure (SD) – mmHg	112(11)	113(11)	112(11)
Mean Diastolic Blood Pressure (SD) - mmHg	66(8)	66(8)	66(8)
Hypertension History	6 (0.8%)	5 (0.5%)	11 (0.6%)
Family History of Hypertension	241 (30%)	361 (33%)	602 (32%)
Antihypertensive use	3 (0.4%)	2 (0.2%)	5 (0.3%)
DTG duration - days	233 [17 - 586]	--	233 [17 - 586]
DTG exposure			
<28 days	226 (28%)	--	226 (28%)
28 – 182 days	140 (18%)	--	140 (18%)
>182 days	429 (54%)	--	429 (54%)

All measures are reported as medians [IQR] and percentages unless mentioned otherwise

ORCHID

J. Jao, CROI 24

Figure 1. Plot of mean (SD) systolic blood pressure (SBP) and diastolic blood pressure (DBP) during gestation until 6 weeks postpartum

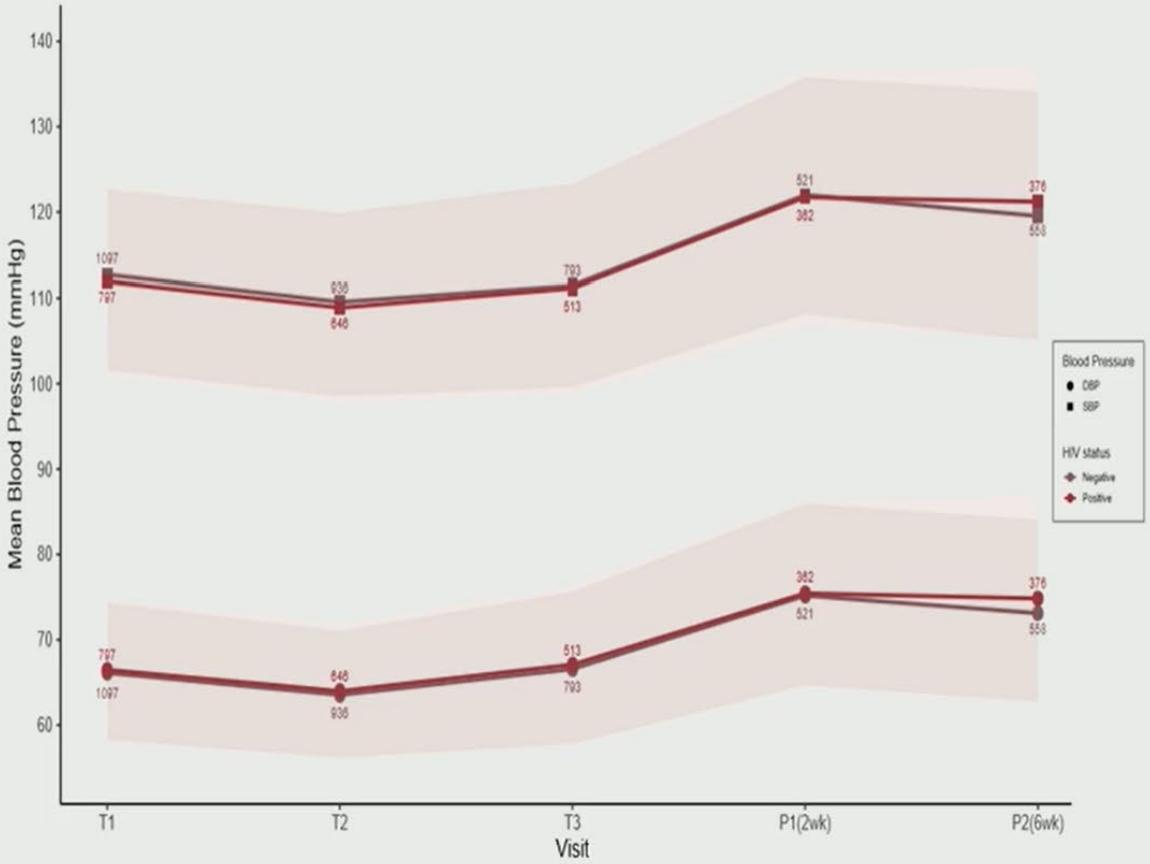

Table 2. Crude and adjusted hazard ratios from cox proportional hazards models assessing the association between incident hypertension and HIV status

Characteristic	Univariate analysis			Multivariate analysis*		
	HR	95% CI	p-value	HR	95% CI	p-value
HIV status						
Negative	Ref	--	--	Ref	--	--
Positive	1.44	1.00 - 2.08	0.051	1.20	0.82 - 1.76	0.4
Age	1.07	1.04 -1.10	<0.01	1.05	1.21 - 1.09	<0.01
BMI greater than or equal to 30 kg/m^2						
No	Ref	--	--	Ref	--	--
Yes	2.23	1.51 - 3.29	<0.01	1.58	1.05 - 2.39	0.03
Gestational age less than or equal to14 weeks						
No	Ref	--	--	Ref	--	--
Yes	0.35	0.23 - 0.54	<0.01	0.32	0.20 - 0.49	<0.01
Current smoker						
No	Ref	--	--	Ref	--	--
Yes	1.31	0.66 - 2.59	0.4	1.47	0.74 - 2.92	0.3
Family History of hypertension						
No	Ref	--	--	Ref	--	--
Yes	1.12	0.77 - 1.64	0.5	1.16	0.79, 1.70	0.5

HR: Hazard Ratio; CI: Confidence Interval
*Model adjusted for baseline systolic and diastolic blood pressures

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Hypertension in Pregnant Persons by HIV Status and by DTG vs EFV Use in Botswana

Denise L. Jacobson *Harvard University, Cambridge, MA, USA*

Could DTG increase hypertensive disorders of pregnancy (HDP)?

- HDP is important cause of adverse maternal/fetal outcomes[1,2]
- Obesity and excess gestational weight gain increase risk of HDP
- Weight gain and obesity increase in women after initiating dolutegravir (DTG)[3]
- Gestational weight gain higher on DTG than efavirenz (EFV)[4,5]

[1]Fokom-Domgue J Clin Hypertens 2015, [2]Gemechy KJ Women's Health 2020, [3]Venter Lancet HIV 2020, [4]Caniglia eClin Med 2020, [5]Chinula et al CROI 2020

Aims:

1) Using Botswana-based Tsepamo Study database, we compared the prevalence of chronic hypertension and risk of HDP in: a) PWHIV on DTG at conception, b) PWHIV on EFV at conception, and c) pregnant persons without HIV
2) We also determined if the relative risk of HDP between groups varied by maternal weight early in pregnancy

Inclusion criteria:

- PWHIV on DTG or EFV started 6 mos-5 yrs before conception, or without HIV
- Had an antenatal care (ANC) visit < 20 weeks gestational age (GA)

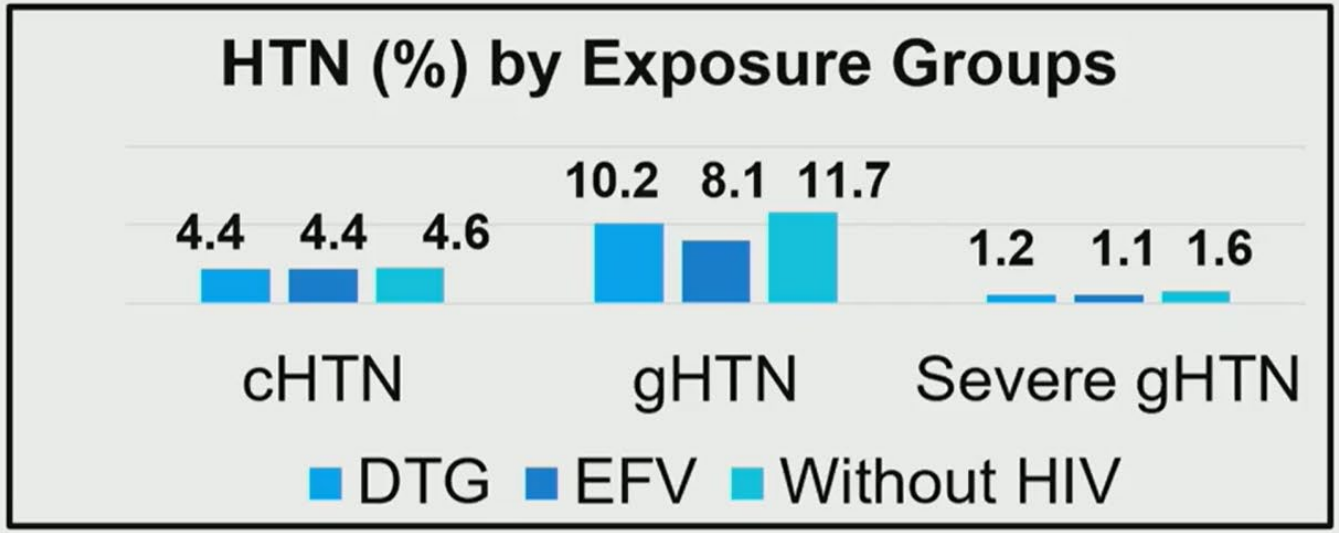
Results:

Maternal characteristics similar in **DTG (N=5866)** vs. **EFV (4771)**

- Age and parity were lower in those **without HIV (N=117309)**

HTN Results:

- cHTN similar by group
- gHTN: 20% lower in EFV v. DTG; 20% higher in those without HIV v. DTG



Relative risk (RR) of HTN outcomes[1]

	gHTN	Severe gHTN
EFV vs DTG	0.80 (0.71, 0.91)	0.91 (0.64, 1.29)
w/o HIV vs DTG	1.20 (1.10, 1.30)	1.56 (1.24, 1.98)

[1]Adjusted for age, marital status, education, parity and tertiary care facility.

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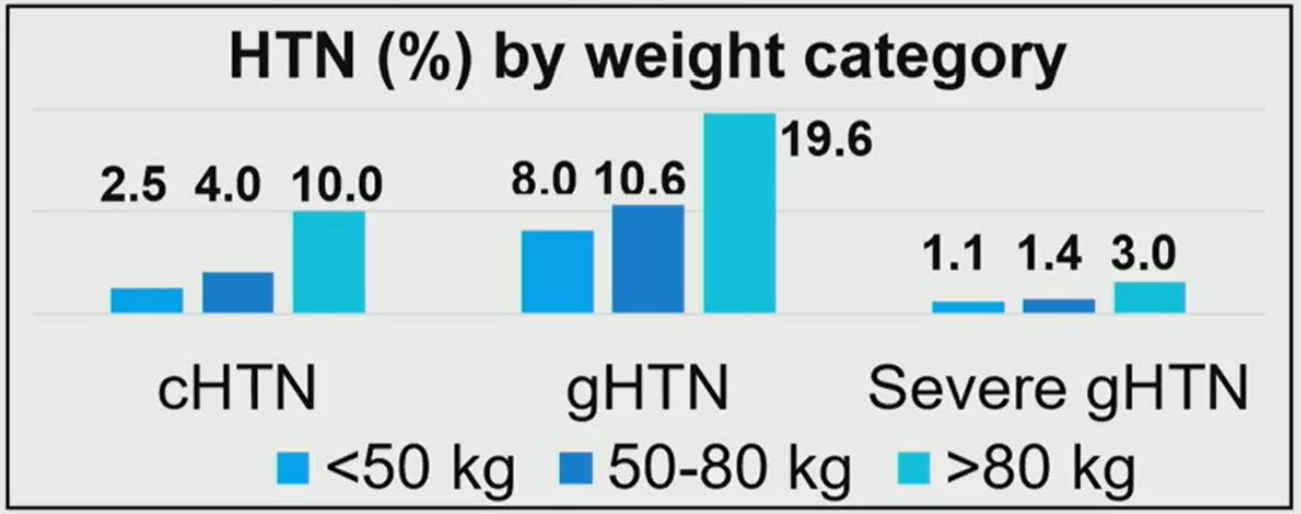
Results (cont)

Percent (%) with weight > 80 kg by age category

Age (yr)	DTG	EFV	Without HIV
< 25	4.6	5.0	5.9
25-29	13.7	10.7	15.9
30-35	21.9	18.2	26.2
>35	27.7	21.0	34.8

HTN more common in highest weight group (>80 kg)

- 10.0% cHTN
- 19.6% gHTN
- 3.0% severe gHTN



Relative risk of HDP between exposure groups did not vary by early maternal weight.

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Limitations

- BP collected during routine care, not a standardized schedule
- Definitions of HTN based on a single measure may overestimate risk

Conclusions

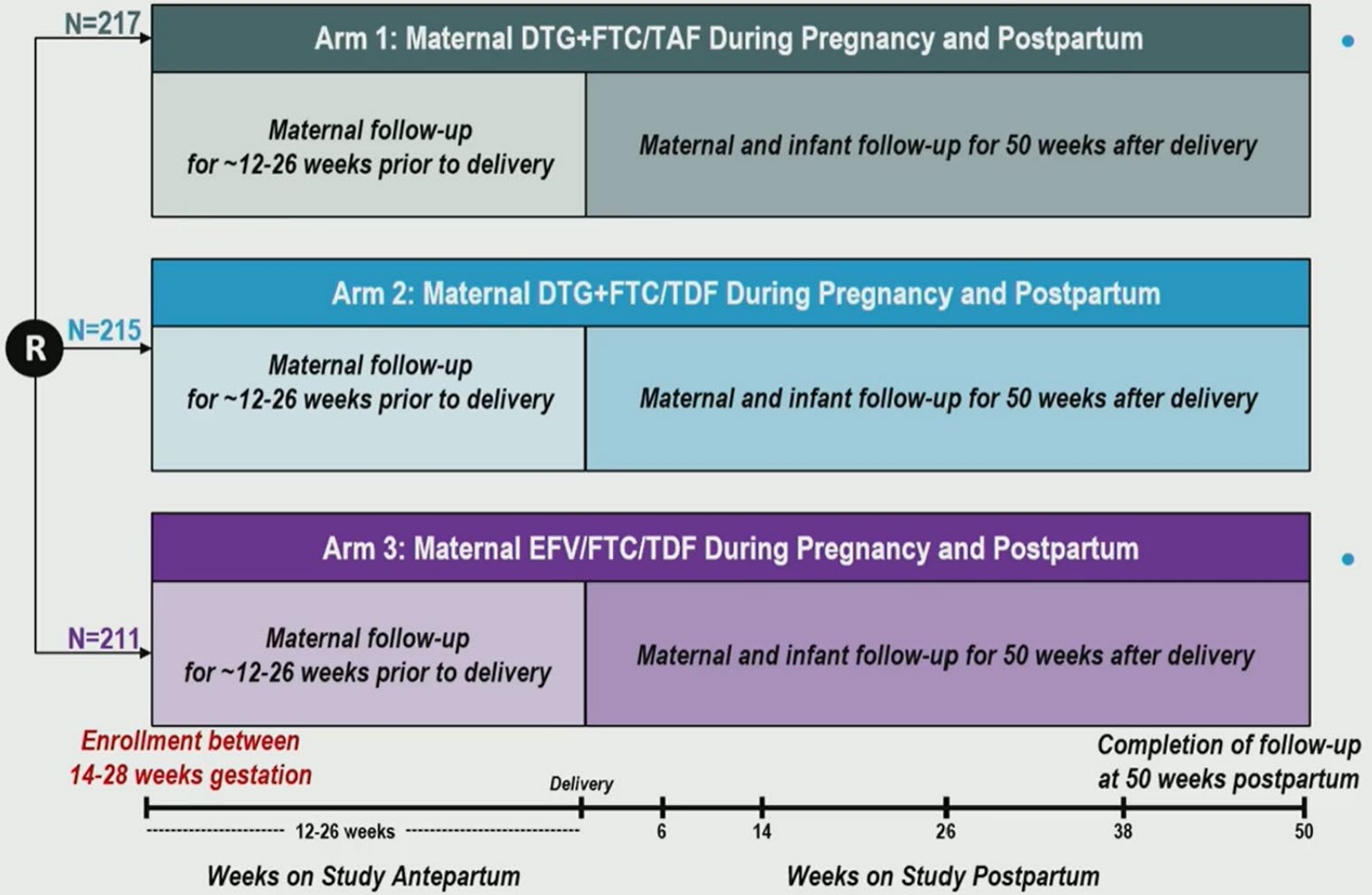
- Chronic HTN: similar prevalence across all exposure groups
- Gestational HTN: more common among PWHIV on DTG at conception than EFV at conception, but less common in both groups compared to those without HIV

Future research needed to…

- Understand if differences are mediated by early weight in pregnancy
- Evaluate the impact of HDP on adverse pregnancy outcomes

Investigators: Denise L. Jacobson, Modiegi Diseko, Judith Mabuta, Ellen Caniglia, Kathleen M. Powis, Lynn M. Yee, Joseph Makhema, Shahin Lockman, Roger Shapiro and Rebecca Zash. Thank you to all participants, staff, funders and the Health Ministry of Botswana

IMPAACT 2010 (VESTED) Background

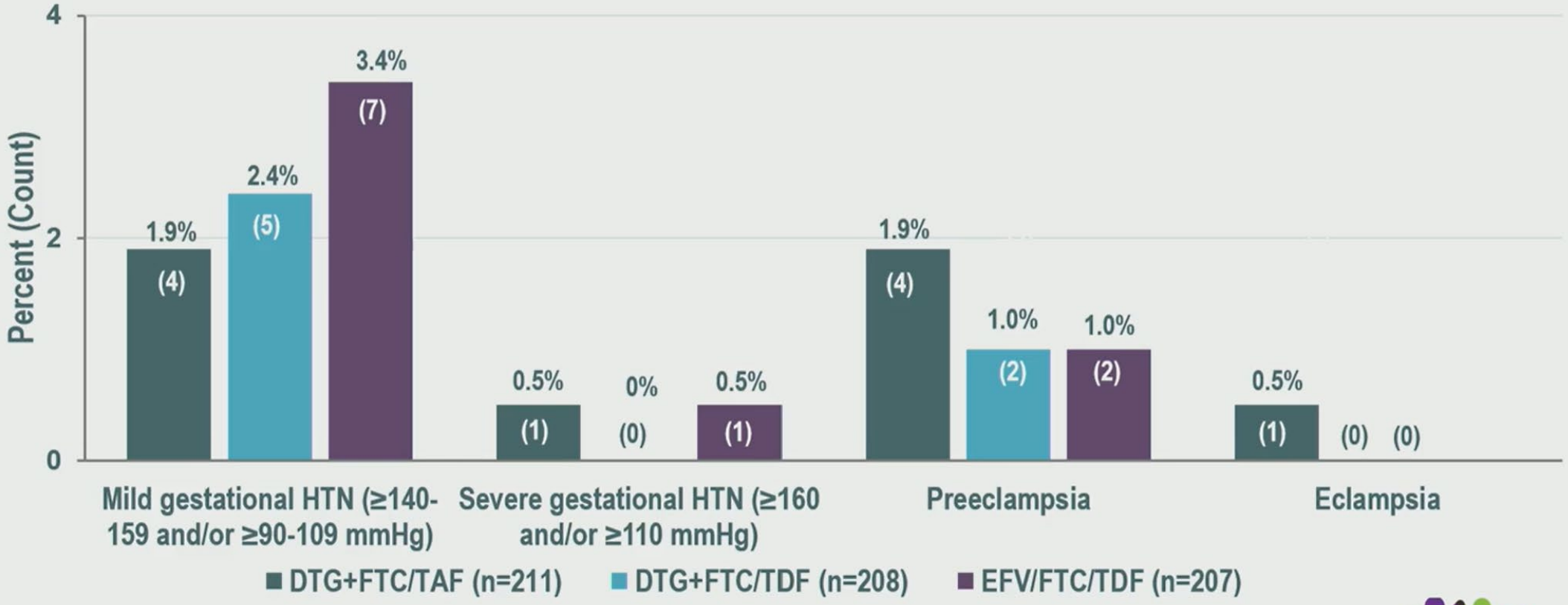


- **Enrolled at 22 sites in 9 countries** (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, US, Zimbabwe) (N=643)
- ***Post-hoc analysis of blood pressure (BP) data over the study period***

Lockman et al, Lancet April 2021; Chinula et al, Lancet HIV June 2023

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Results: Gestational hypertension (HTN), preeclampsia, and eclampsia



Preeclampsia/eclampsia based on site report of diagnosis and not standardized across the study

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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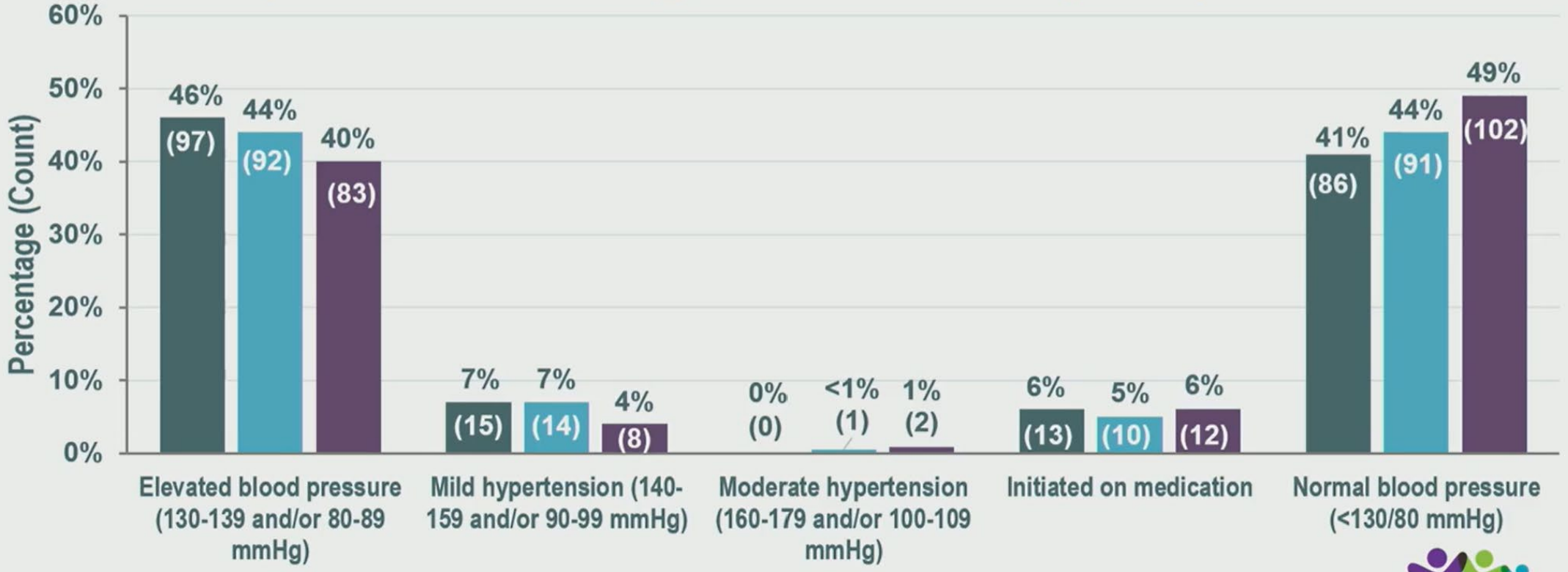
Results: Occurrence of elevated blood pressure and incident mild or worse hypertension by arm, antepartum through 50 weeks postpartum



No cases of severe hypertension observed

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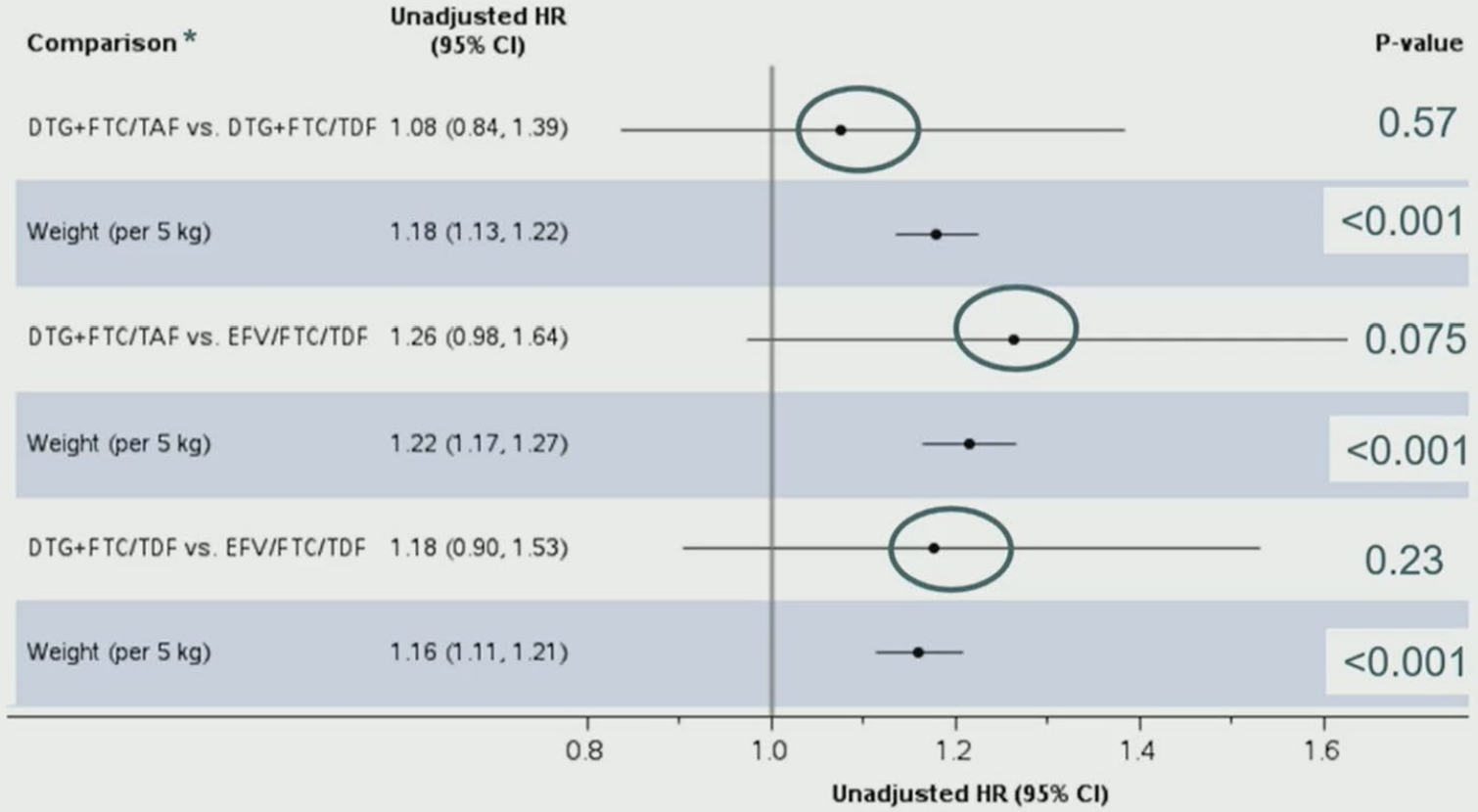
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

R. Hoffman, CROI 24

Results: Hazard ratios for occurrence of elevated blood pressure and incident hypertension by arm, antepartum through 50 weeks postpartum



- Independent of treatment:
  - For every 5 kg increase in weight: ≈16-22% increase in the hazard of elevated blood pressure or mild or worse hypertension
- Non-significant trend for increased hazard in by-arm comparisons, more notable for DTG+FTC/TAF vs EFV/FTC/TDF

*HRs for by-arm comparisons were similar when adjusted for weight

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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TAKE HOME: Reassuring!!
Pre-pregnancy weight optimisation

Neonates & Children

- ART in paediatric population

Long-Acting Cabotegravir Plus Rilpivirine In Adolescents With HIV: Week 24 IMPAACT 2017(MOCHA) Study

Aditya Gaur *St Jude Children's Research Hospital, Memphis, TN, USA*

- Watch Tristan’s session!

ART-Free HIV-1 Remission in Very Early Treated Children: Results From IMPAACT P1115

Deborah Persaud *The Johns Hopkins University School of Medicine*

IMPAACT P1115 is designed to investigate whether very early ART for neonates would limit HIV-1 reservoirs sufficiently to observe at least one case of ART-free remission, as in "The Mississippi Baby".

IMPAACT P1115 Study Participants

30 clinical research sites in 11 countries

54 neonates with confirmed in utero HIV-1 received very early ART≠ within 48 hours of life

↓

6 children met eligibility criteria and discontinued ART for analytic treatment interruption **(ATI)**

Year of Enrollment:
2015-2017

Age at ATI:
Median 5.5 years instead of at least 2 years as planned due to delays with COVID-19

≠Very early nevirapine-based ART or a three-drug nevirapine (NVP) prophylactic regimen with transition to three-drug NVP-ART regimen within 10 days of birth;
LPV/r added when age-appropriate ([min, max]: ***15-29 days of age***
NVP discontinued 12 weeks after achieving two consecutive HIV-1 RNA <LOD [min, max]:***17-29 weeks of age***

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Lancet HIV 2020, 2023

Eligibility for ATI to Evaluate for ART-free Remission

Pre-ATI Criteria

Plasma viral load <200 c/mL by study week 24

Sustained undetectable plasma HIV-1 RNA from week 48 onwards

- No subsequent HIV-1 RNA detected through time to ATI

Cessation of breastfeeding

- At least six weeks prior to evaluation for ATI

Parent or legal guardian willing and able to provide informed consent

Pre-ATI Biomarker Profile

Normal CD4+ T cell count for age and CD4+ T cell percentage ≥25

Negative HIV-1 antibody status

- Tested on two consecutive samples collected at least 8 weeks apart
- Determined with 4th generation ELISA

No HIV-1 DNA detected in ≥850,000 PBMCs

- Tested on two consecutive samples collected at least 8 weeks apart
- Determined with a CLIA-certified, pan-subtype droplet digital PCR HIV-1 DNA assay

ART-free remission: *no confirmed plasma HIV-1 RNA above the limit of detection (LOD) of the assay for ≥48 weeks off ART*

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Lancet HIV 2020, 2023

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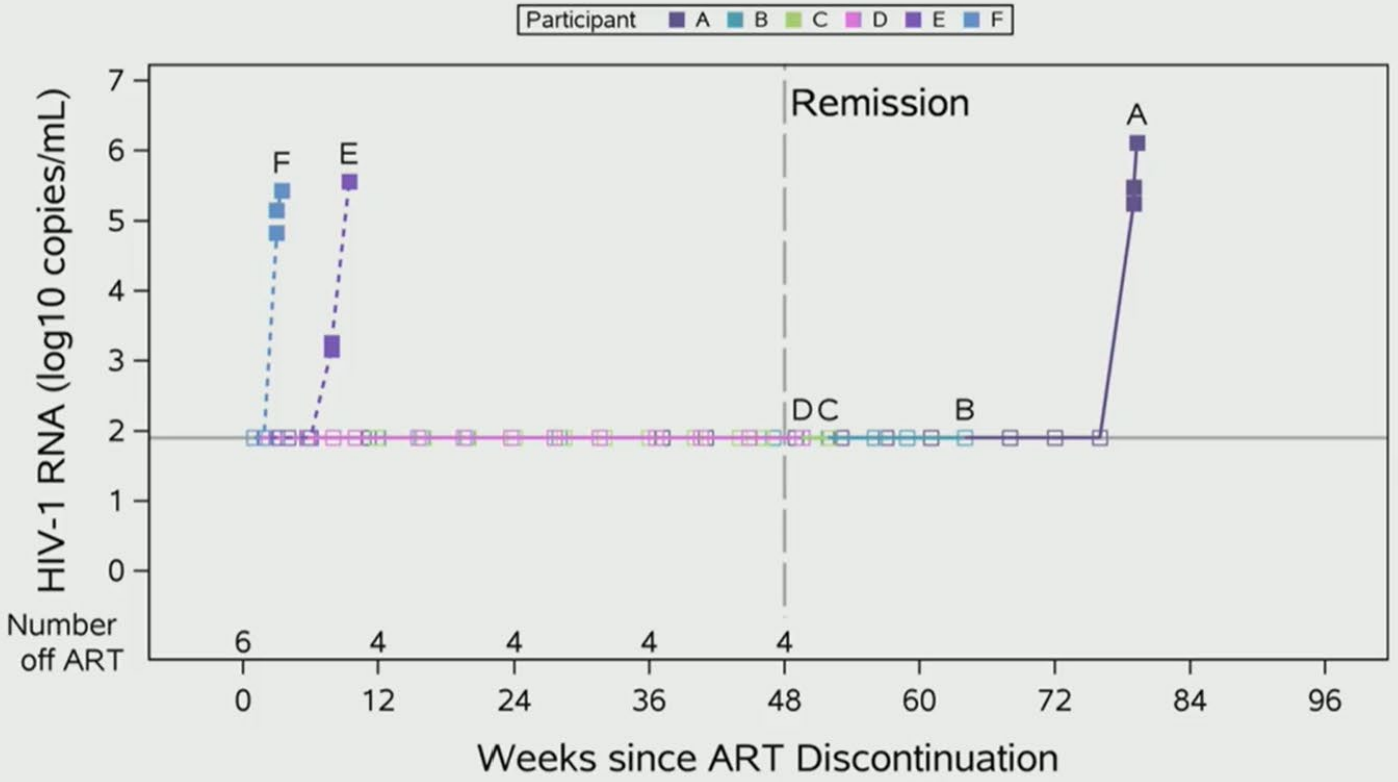
Sustained Aviremia off ART (ART-free Remission)

Study Weeks off ART
(no detectable plasma HIV-1 RNA)

A	80
B	>64
C	>52
D	>48
E	8
F	3



4 of 6 very early treated children with durable virologic suppression achieved ART-free remission with **no viremic rebound for ≥48 weeks** (exact 95% CI 22%-96%)

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Summary and Conclusions

- This study provides **proof-of-concept** that very early ART in neonates with in utero HIV-1 significantly curtailed viral reservoirs and enabled ART-free remission.
  - The proposed eligibility criteria and biomarker profiling was not fully predictive of ART-free remission, as evidenced by rebound in two of six children who underwent ATI.
  - The occurrence of acute retroviral syndrome with rebound viremia warrants careful clinical oversight during ATI.

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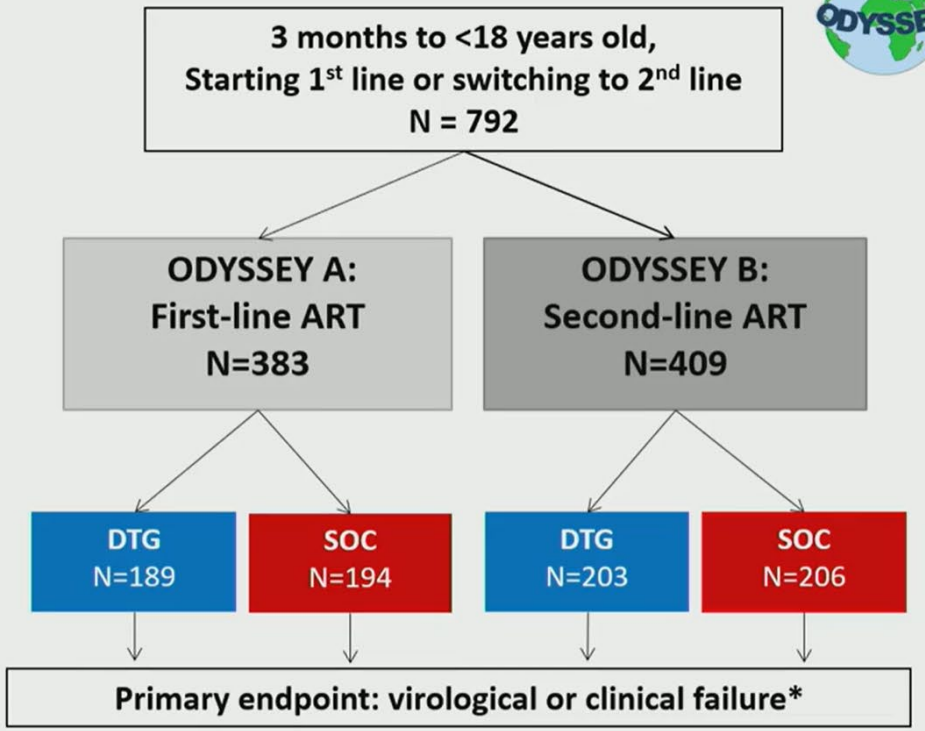
ODYSSEY 192-Week Follow-Up Evidences Superior Efficacy of DTG for Children on First/Second-Line ART

Hilda A. Mujuru *University of Zimbabwe*

ODYSSEY

- ODYSSEY compared DTG to non-DTG standard-of-care (SOC) in children. Here we present 192 week follow-up
- **Randomised follow-up** until last participant reached week 96
- **Extended follow-up:** 683 participants in Thailand and Africa consented to extended follow-up (97% of 707 approached). Children in SOC arm switched to DTG according to country guidelines/clinician decision
- Total median follow-up 5.5 years (IQR: 4.5-6.0)



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*Virological failure: confirmed (x2) VL ≥ 400 c/mL at any time after w36, or insufficient virological response <1 log drop at w24 and ART switch for treatment failure. Clinical failure: any new or recurrent severe WHO 3 or WHO 4 event, or death due to any cause.

Population at baseline (N=792)

Characteristics

- 707 in ≥14kg, 85 in <14kg cohort
- Age, median [range]: 11.4 years [0.1-18]
- Weight, median [range]: 29kg [3.4-85]
- 49% female
- 28% WHO stage 3/4
- 31% CD4% <15%

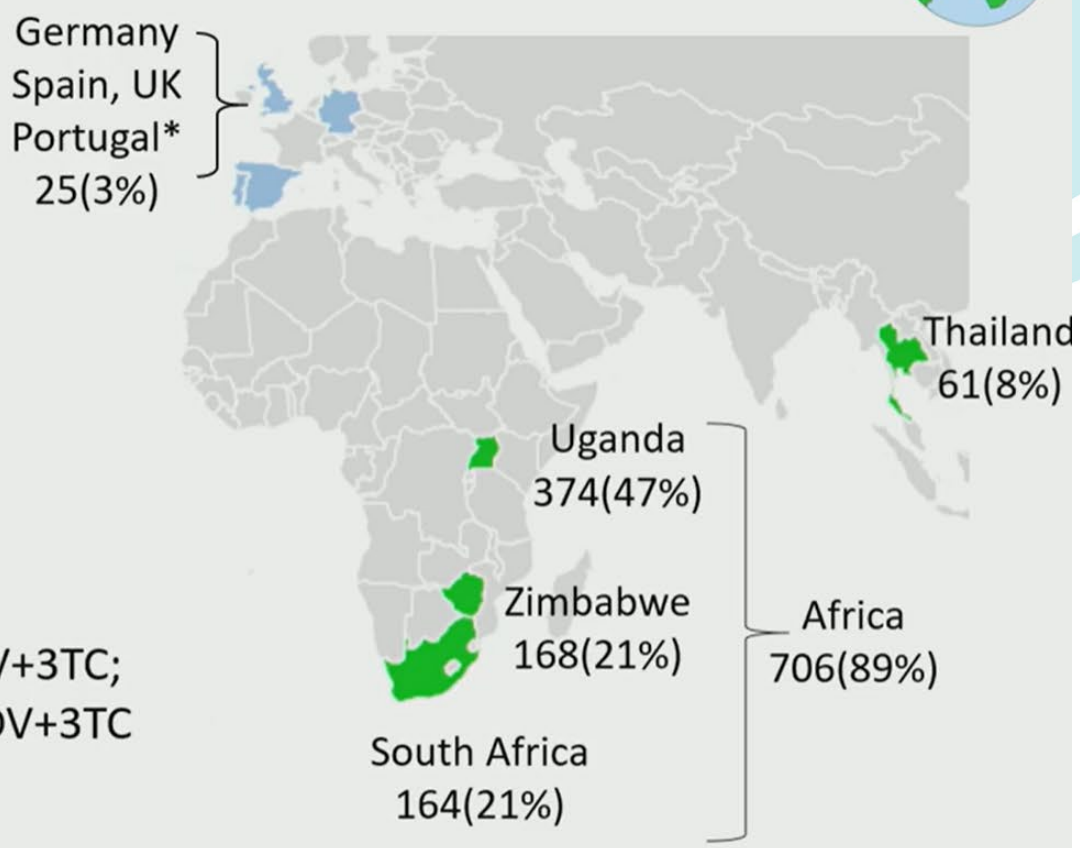
Baseline ART in ODYSSEY at randomisation

NRTIs were balanced across the arms

- ODYSSEY A: **83% ABC+3TC**, 16% TDF+XTC~, 1% ZDV+3TC;
- ODYSSEY B: **54% ABC+3TC**, 25% TDF+XTC~, 20% ZDV+3TC

Third agent in SOC

- ODYSSEY A: **81% NNRTI**, 19% bPI, 1% INSTI
- ODYSSEY B: 3% NNRTI, **96% bPI**, 1% INSTI



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*Participants in Germany, Spain, UK and Portugal only followed during randomised phase
~ 1 ODYSSEY A SOC and 1 ODYSSEY B SOC participant initiated TAF+FTC

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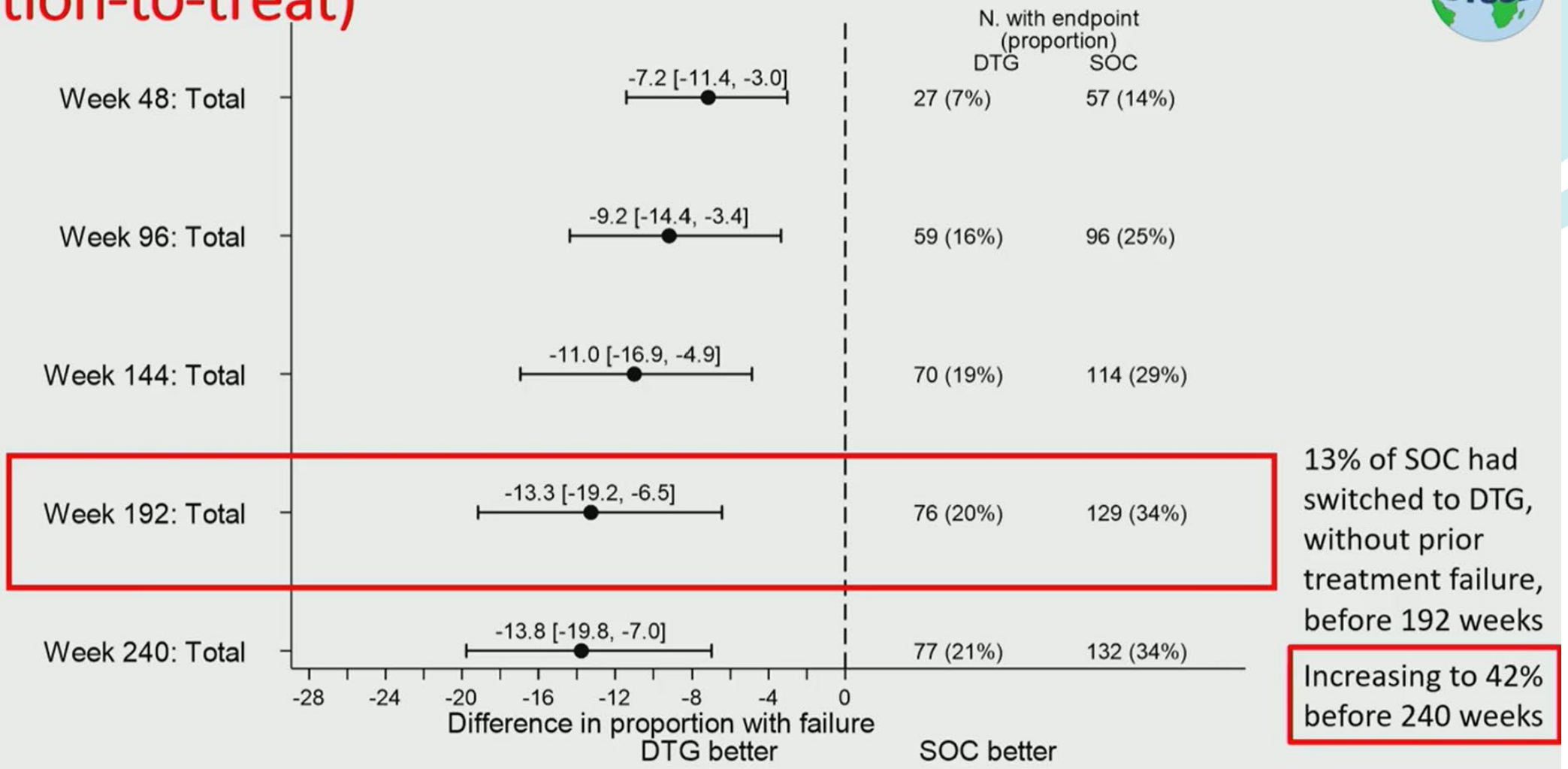
Virological or clinical failure by follow-up week (intention-to-treat)



13% of SOC had switched to DTG, without prior treatment failure, before 192 weeks

Increasing to 42% before 240 weeks

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This finding maintained when disaggregated for A vs B and Weight <14kg and >14kg

H. Mujuru, CROI 2024

Summary of adverse events to week 192 (intention-to-treat)

	Total: ODYSSEY A + ODYSSEY B						
	DTG		SOC		Total		P-value+
Participants randomised	392		400		792		
N adverse events (AE) [N participants]							
Serious adverse events#	85	[52]	66	[53]	151	[105]	0.98
AEs grade 3 or above	157	[98]	192	[121]	349	[219]	0.10
ART-modifying AEs	8	[7]	24	[21]	32	[28]	0.008
Neurological AEs	6	[6]	8	[6]	14	[12]	0.97
Psychiatric AEs^	14	[12]	8	[5]	22	[17]	0.08

82% serious adverse events were hospital admissions

^ 19 psychiatric AEs were in randomised follow-up (described in *Turkova, 2023*[1]); three additional in extended follow-up (two aggressive/violent behaviour in DTG; parasuicide in SOC)

+ Comparing number of children with at least 1 event using Mantel-Haenszel Chi-squared test

[1]Turkova, 2023, The Lancet Child & Adolescent Health, Volume 7, Issue 10, 718 - 727

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Summary

- Superior efficacy of DTG-based ART versus SOC up to 192 weeks in children starting first- or second-line ART, and in children enrolled ≥14kg and <14kg
- Safety reassuring, with no difference in serious or severe adverse events
- More psychiatric adverse events in the DTG arm; small numbers, nearly all in first 2 years of treatment
- Nearly all (99%) children in SOC switched to DTG by the end of the EFU
- After switch to DTG, 90% of SOC participants were suppressed <400c/mL
- Results strongly support transition of children to DTG-based regimens
- On average, for every 8 children treated with DTG versus alternative ART, one treatment failure will be prevented over 192 weeks

Penta

H. Mujuru, CROI 2024

TAKE HOME: Reassuring!!

One to watch: *(When made open access)*

Cardiometabolic Risks and Complications: Adolescents and Young Adults With Perinatally Acquired HIV

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