



Increasing second-line ART options for children with HIV in Africa: week-96 efficacy and safety results of the CHAPAS*-4 randomised trial

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**CHAPAS 4: Children with HIV in Africa – Pharmacokinetics and Acceptability of Simple second-line ART*



Background



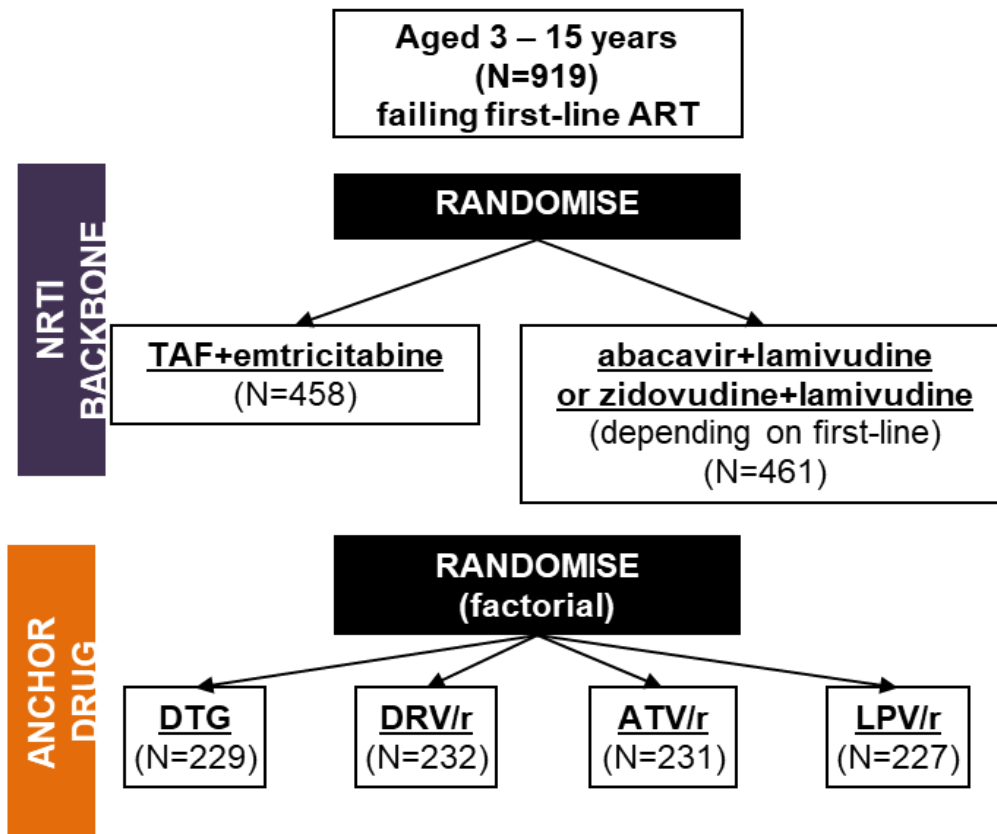
- Limited options & formulations for second-line ART for children living with HIV
 - Lopinavir/ritonavir (LPV/r) needs to be taken twice-daily
 - Very few data on Tenofovir alafenamide (TAF) in children
- CHAPAS-4 (ISRCTN22964075) evaluated long-term outcomes for children switching from first-line ART (NNRTI-based) to second-line ART:
 - NRTI backbone
 - Anchor drugs



CHAPAS-4 Design and Drugs



CHAPAS-4
Children with HIV in Africa: Pharmacokinetics and Acceptability of Simple novel second-line antiretroviral regimens



Factorial 4X2 Open-Label Trial

- **NRTI** backbone randomisation:

- TAF/FTC OD
- abacavir (ABC) or zidovudine (ZDV) with lamivudine (3TC) (standard-of-care, SOC)

- **Anchor** drug randomisation:

- dolutegravir (DTG) OD,
- darunavir (DRV/r*) OD
- atazanavir (ATZ/r*) OD
- lopinavir (LPV/r*) BD

- All dosed according to WHO weight-bands
- PK and toxicity sub-studies

*ritonavir (100mg & 25mg tabs)



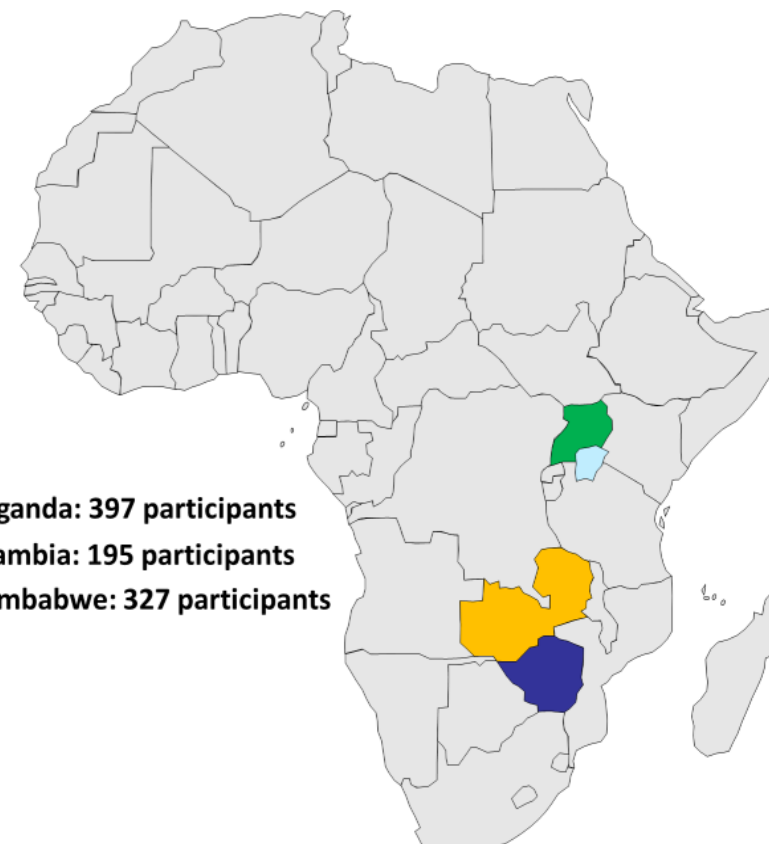
Hypotheses and methods

- Primary endpoint: viral load (VL) <400 copies/mL at week 96*
- Hypotheses:
 - TAF/FTC non-inferior to ABC or ZDV (SOC) (10% margin)
 - ATV/r non-inferior to LPV/r (12% margin)
 - DRV/r superior to LPV/r and ATV/r arms combined**
 - DTG superior to LPV/r and ATV/r arms combined**
- Primary analysis: intention-to-treat
 - Secondary: per-protocol for non-inferiority comparisons listed above

*Death counted as VL \geq 400c/ml

** Superiority threshold $p \leq 0.03$ (as multiple comparisons)

Sites and Population Characteristics (n=919)



		n (%) or median (IQR)	
Male		497	(54%)
Age (years)		10	(8, 13)
WHO stage	1/2	778	(85%)
	3/4	141	(15%)
CD4 (cells/mm ³) (n=906)		669	(413, 971)
VL (copies/ml)		17 573	(5 549, 55 700)
Weight-for-age Z score		-1.6	(-2.4, -0.9)
Height-for-age Z score		-1.6	(-2.3, -0.8)
BMI-for-age Z score		-1.0	(-1.7, -0.4)
First-line NRTI	Abacavir 53%	Zidovudine 47%	
First-line NNRTI	Efavirenz 56%	Nevirapine 44%	
Years on first-line ART		5.6	(3.3, 7.8)

Trial sites

- Uganda: JCRC Kampala, JCRC Mbarara
- Zambia: UTH, ADCH
- Zimbabwe: UZCRC, Mpilo Hospital
- Project coordination: UZCRC
- Trial coordination and communication: MRC CTU at UCL
- Other partners: Radboud University, University of Cape Town, University of York



Treatment and follow-up

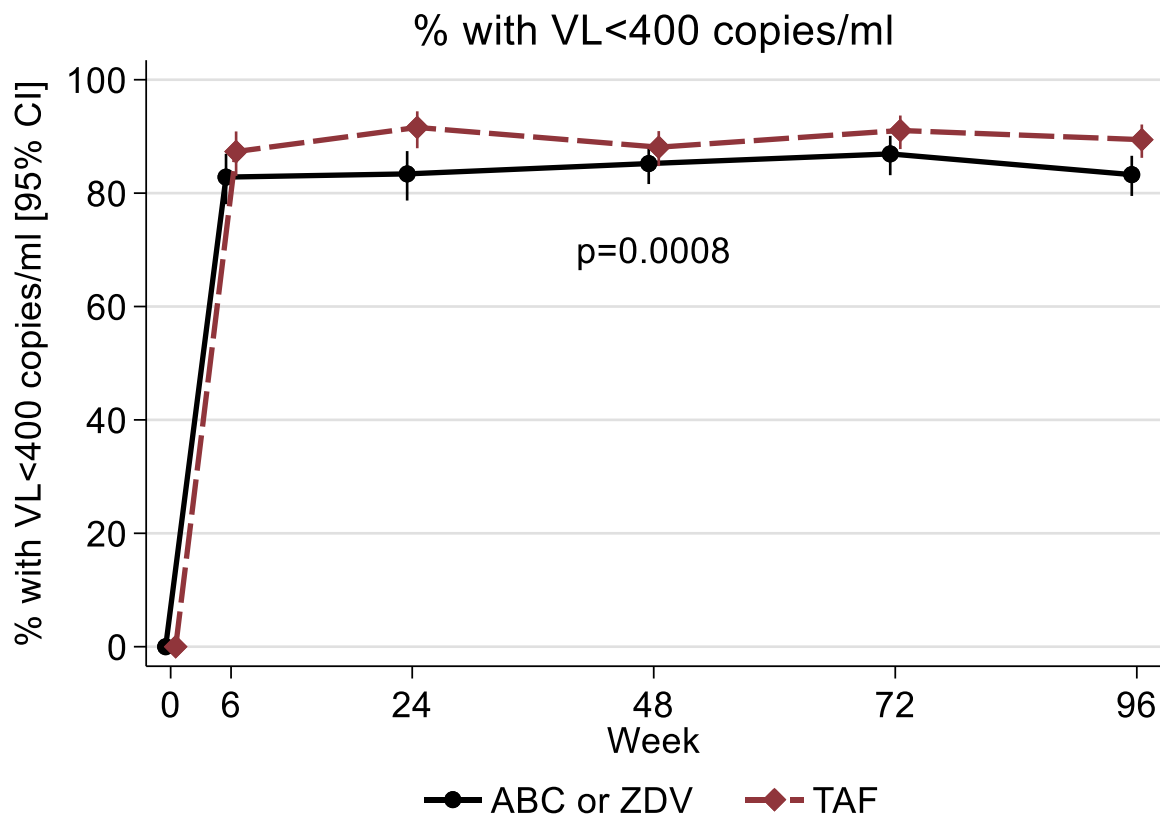
- At randomisation
 - 100% (919) started randomised **NRTI** backbone
 - 99% (910) started randomised **anchor** drug*
- Over 96 weeks
 - 99% visits completed
 - **11 (1.2%) lost to follow-up**
 - 98% time on allocated regimen
 - 5 (0.5%) started third-line

* 8 protocol-planned modifications for TB, 1 error (corrected week 2)

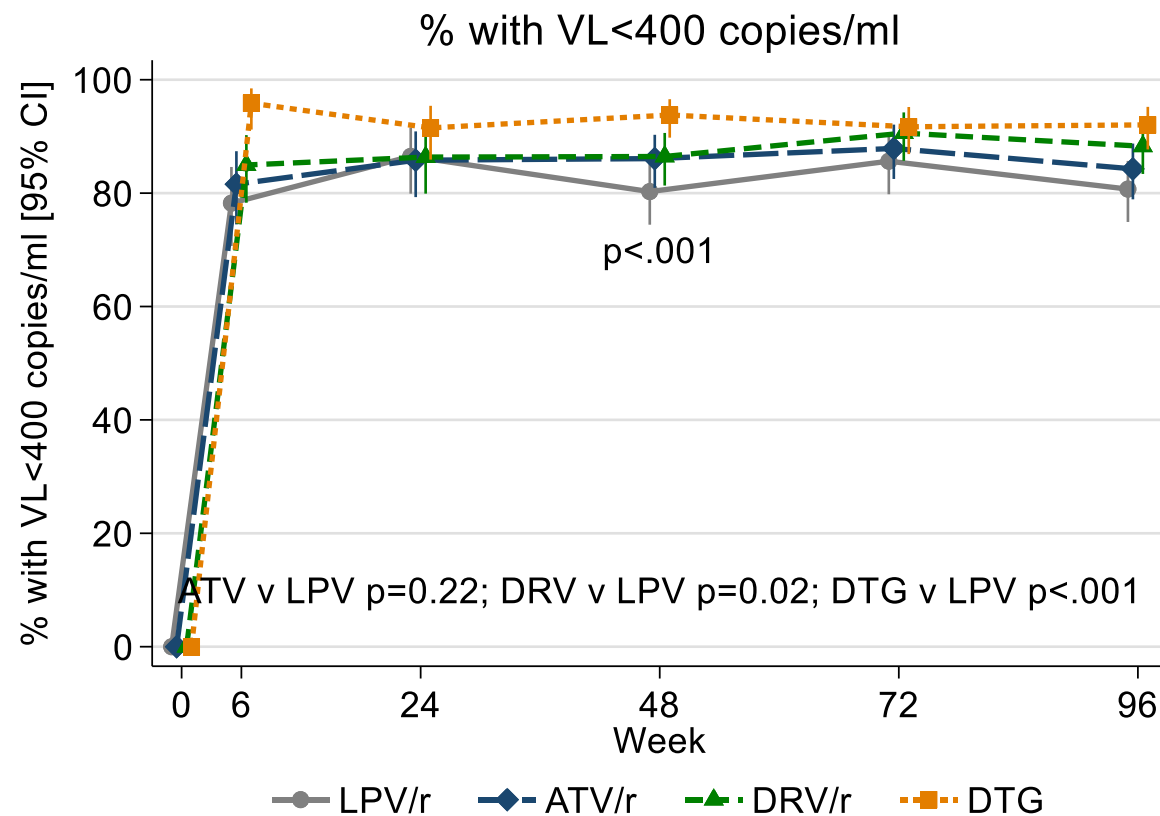
Results: VL < 400 c/ml

- VL suppression was high in all arms

NRTI backbone



Anchor drug



Week 96 VL <400 c/ml (primary endpoint)

- TAF/FTC (89.4%) superior to ABC or ZDV (SOC) backbone (83.3%)
- ATV/r (84.3%) non-inferior to LPV/r (80.7%)
- DTG (92.0%) superior to LPV/r & ATV/r (82.5%)
- DRV/r (88.3%) showed a trend to superiority to LPV/r & ATV/r (82.5%)

Drugs compared	Difference (%) [95% CI]		p value
TAF - ABC or ZDV	6.3	[2.0, 10.6]	0.004
ATV/r - LPV/r	3.4	[-3.4, 10.2]	0.33
DTG - LPV/r or ATV/r	9.7	[4.8, 14.5]	<0.0001
DRV/r - LPV/r or ATV/r	5.6	[0.3, 11.0]	0.04*

*p value higher than the prespecified value of 0.03

Other viral load endpoints

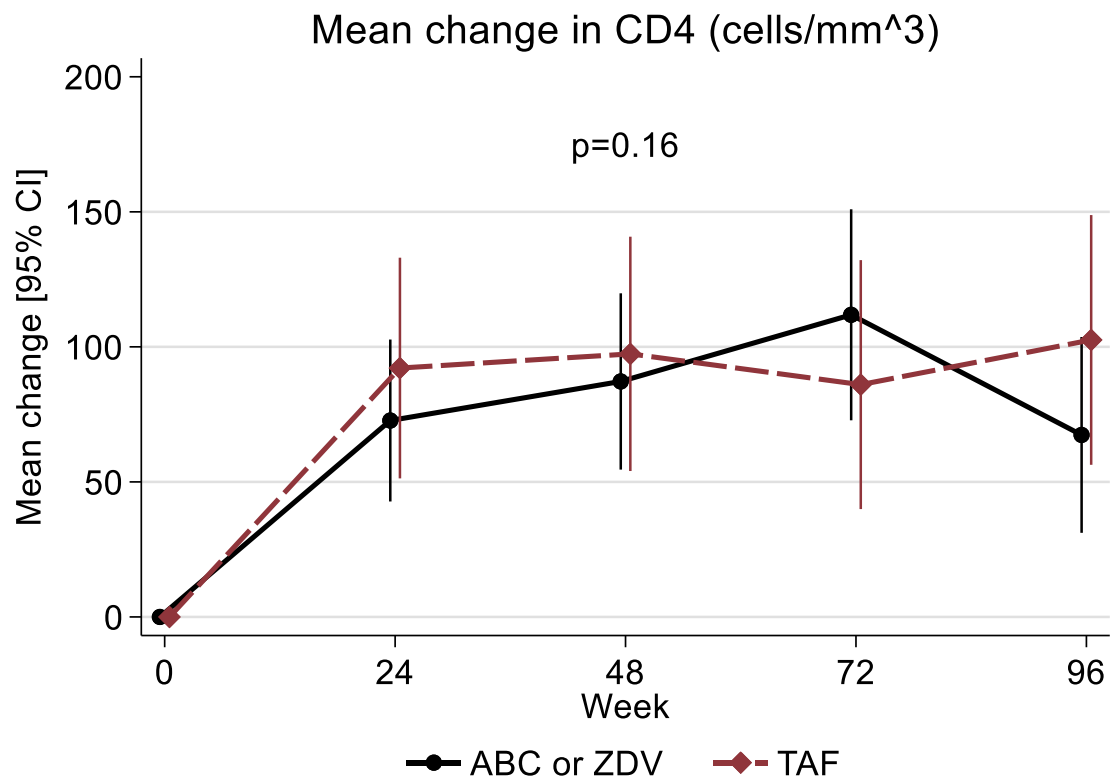
- **NRTI** backbone and **anchor** drug effects similar for
 - VL <60 and <1000 copies/ml (week 96)
 - VL <400 (week 48 (n=907), and week 144 (n=488))
 - Per-protocol population VL <400 (week 96)
 - Sub-groups VL <400 (week 96), including:
 - First-line NRTIs (ABC-based vs. ZDV-based) ($p_{\text{interaction}} > 0.4$)
 - VL, sex, weight, first-line NNRTI (EFV or NVP), CD4

Week 96	VL <400 c/ml			VL <60 c/ml		VL <1000 c/ml			
	Difference (%)		p	Difference (%)	p	Difference (%)		p	
	[95% CI]			[95% CI]			[95% CI]		
TAF - ABC or ZDV	6.3	[2.0, 10.6]	0.004	6.3	[1.0, 11.5]	0.02	4.6	[0.6, 8.6]	0.02
ATV/r - LPV/r	3.4	[-3.4, 10.2]	0.33	5.4	[-2.5, 13.2]	0.18	2.9	[-3.5, 9.3]	0.37
DTG - LPV/r or ATV/r	9.7	[4.8, 14.5]	<0.0001	10.5	[4.4, 16.6]	0.0007	8.5	[4.1, 13.0]	0.0002
DRV/r - LPV/r or ATV/r	5.6	[0.3, 11.0]	0.04	3.1	[-3.5, 9.8]	0.35	4.9	[0.0, 9.9]	0.048

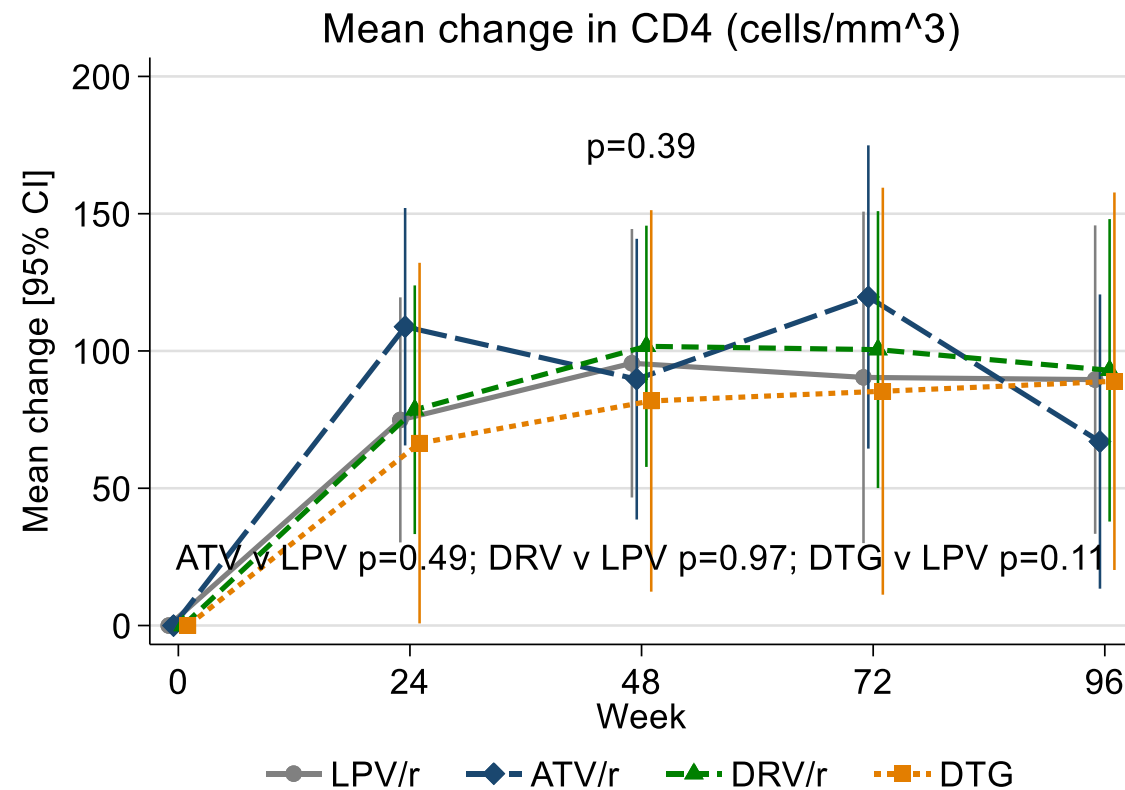
Change in CD4 cell count (median baseline 669 cells/mm³)

- CD4 count increased in all arms
- No evidence of difference for either **NRTI** or **anchor drug** randomisations

NRTI backbone



Anchor drug



- Low rates of AEs overall
- No evidence of difference between ABC or ZDV (SOC) and TAF

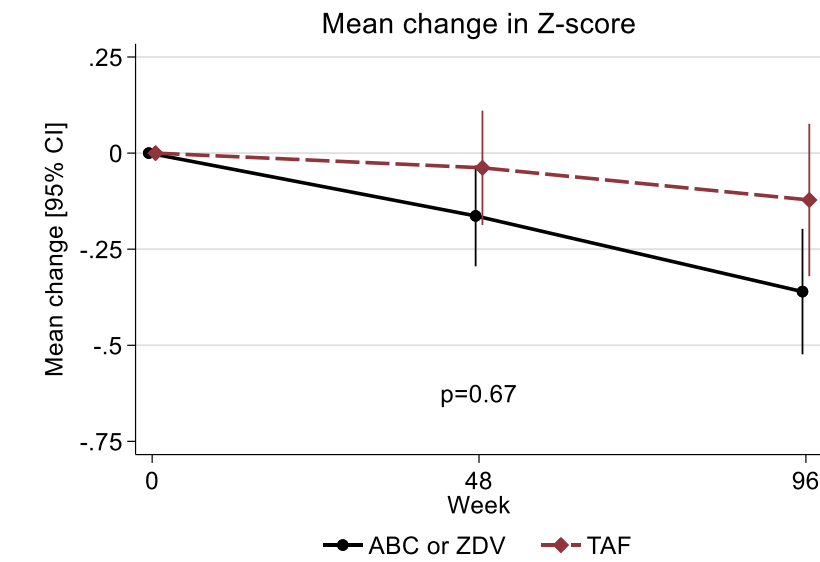
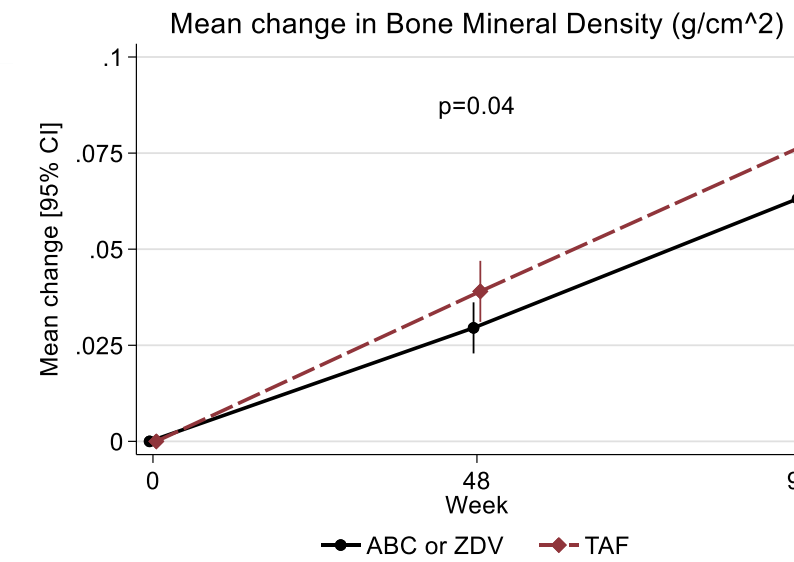
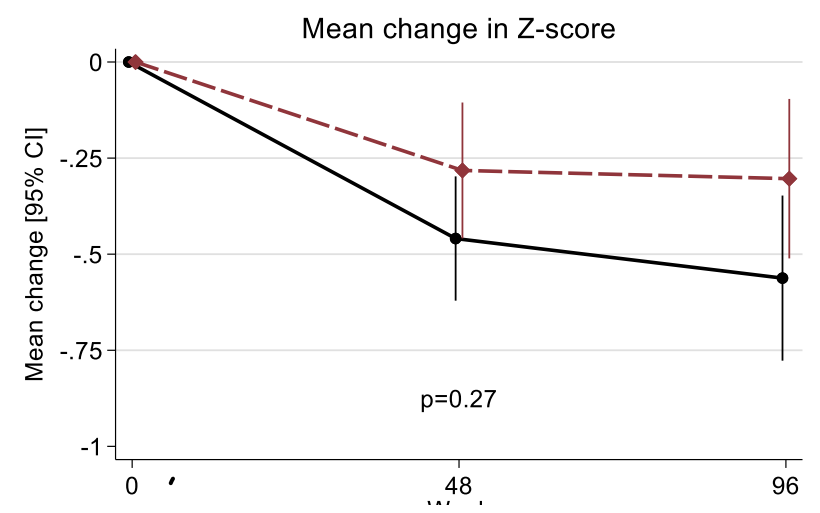
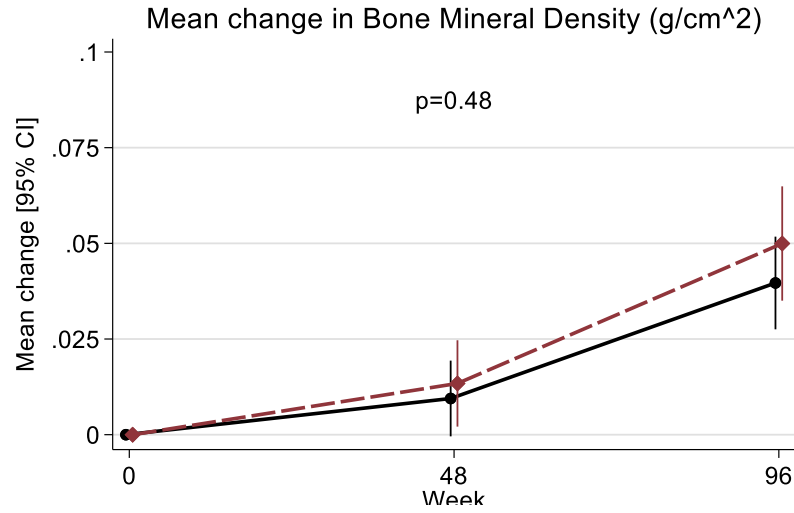
	ABC or ZDV (SOC) N=461			TAF N=458		
	Patients	(% of patients)	Events	Patients	(% of patients)	Events
ART-modifying (any grade) (p=0.84)	12	(2.6%)	21	11	(2.4%)	19
Grade 3/4 (p=0.93)	64	(13.9%)	92	63	(13.8%)	81
SAE (p=0.84)	14	(3.0%)	14	15	(3.3%)	17
Hospitalisation	13	(2.8%)	13	14	(3.1%)	16
Death	0	(0.0%)		1*	(0.2%)	

* Week 12; treatment-unrelated; primary cause: hypotension/shock/toxic shock (secondary: severe malnutrition; candidiasis of oesophagus, trachea, bronchi or lungs)

DEXA scans (n=170): **NRTI** backbone

Lumbar total:
No evidence of difference

Total body less head:
Greater increase in BMD for TAF than ABC or ZDV (SOC) (p=0.04)
No evidence of difference for Z-score



Adverse events: anchor drug

- More grade 3/4 AEs, mostly hyperbilirubinemia, occurred for ATV/r vs. LPV/r
- DTG fewer grade 3/4 AEs vs. LPV/r
- No evidence of difference for ART-modifying events or SAEs

	LPV/r N=227			ATV/r N=231			DRV/r N=232			DTG N=229		
	Patients (% of patients)		Events	Patients (% of patients)		Events	Patients (% of patients)		Events	Patients (% of patients)		Events
ART-modifying (p>0.3)	7	(3.1%)	11	5	(2.2%)	11	4	(1.7%)	8	7	(3.1%)	10
Grade 3/4†	26	(11.5%)	35	69	(29.9%)	92	20	(8.6%)	28	12	(5.2%)	18
Raised bilirubin	1	(0.4%)	1	57	(24.7%)	66	1	(0.4%)	1	0	(0.0%)	0
SAE (p>0.1)	10	(4.4%)	10	5	(2.2%)	6	8	(3.4%)	9	6	(2.6%)	6
Death	0	(0.0%)		0	(0.0%)		0	(0.0%)		1*	(0.4%)	
Hospitalisation	9	(4.0%)	9	5	(2.2%)	6	8	(3.4%)	9	5	(2.5%)	5

† ATV/r vs. LPV/r p<0.0001; DRV/r vs. LPV/r p=0.31; DTG vs. LPV/r p=0.02

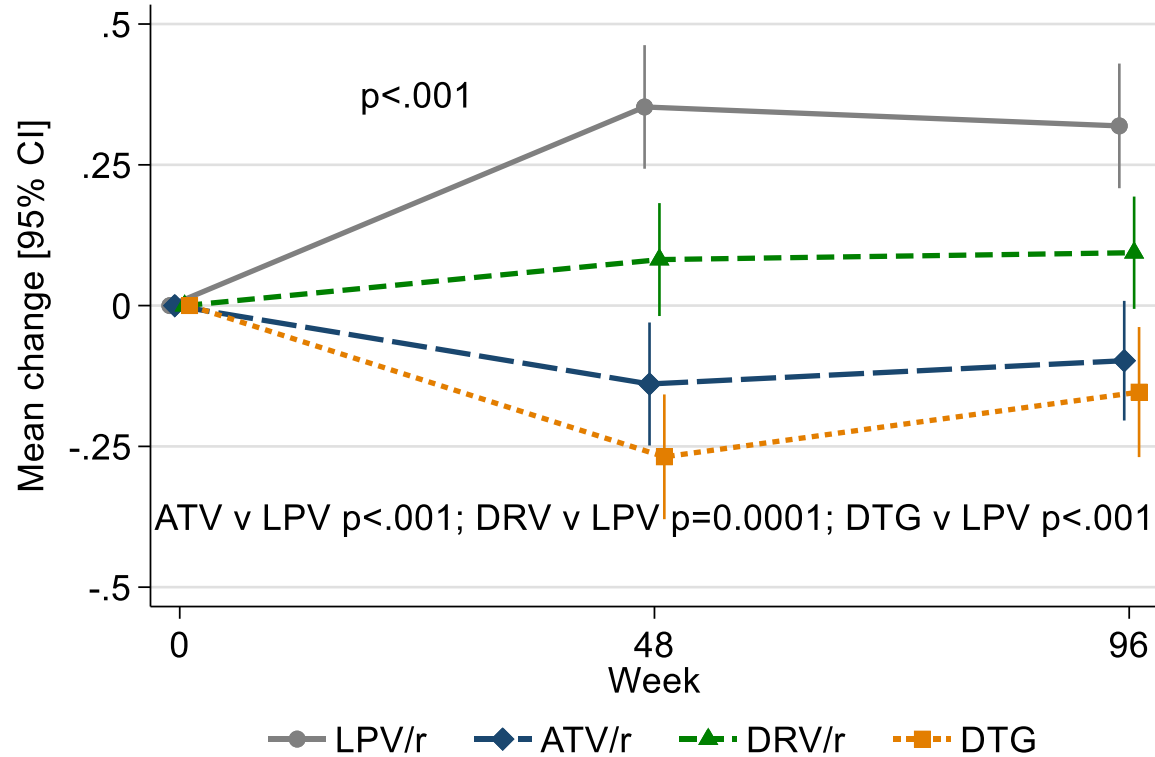
* Week 12; treatment-unrelated

Lipids: anchor drug

Increased total and LDL cholesterol in LPV/r vs other arms

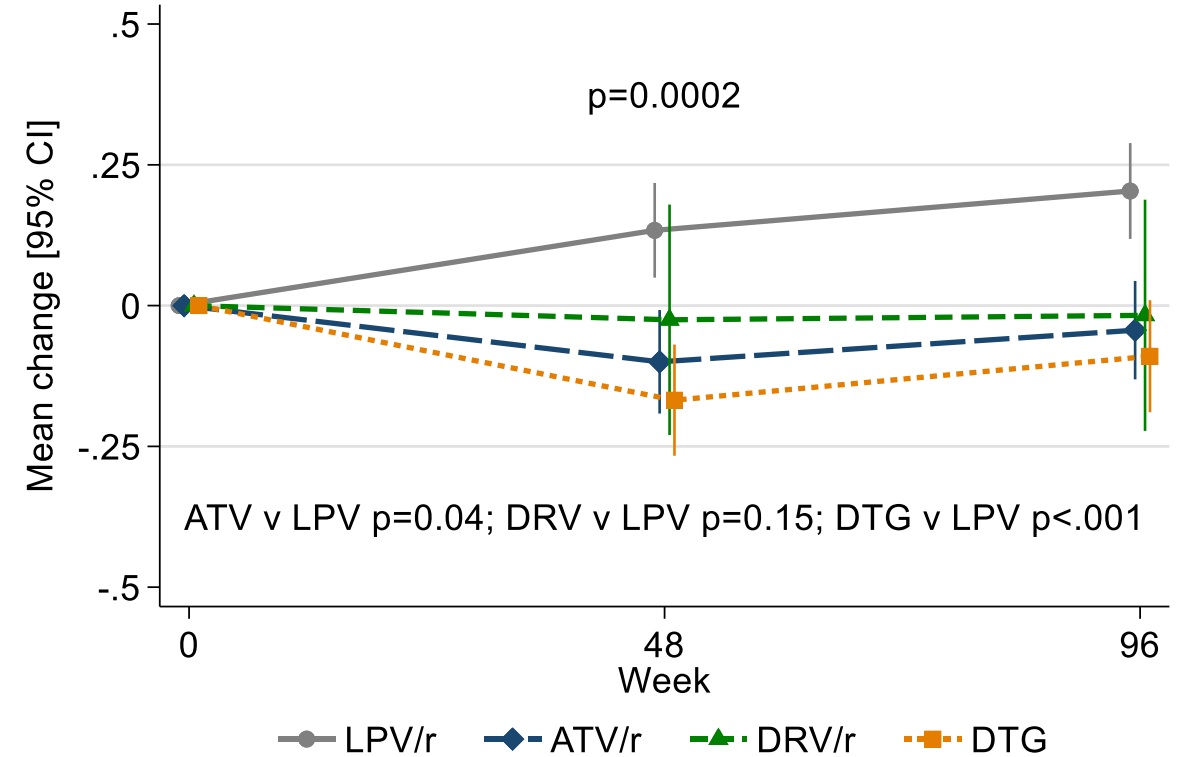
Total Cholesterol

Mean change in Total Cholesterol (mmol/l)



LDL-Cholesterol

Mean change in LDL-Cholesterol (mmol/l)

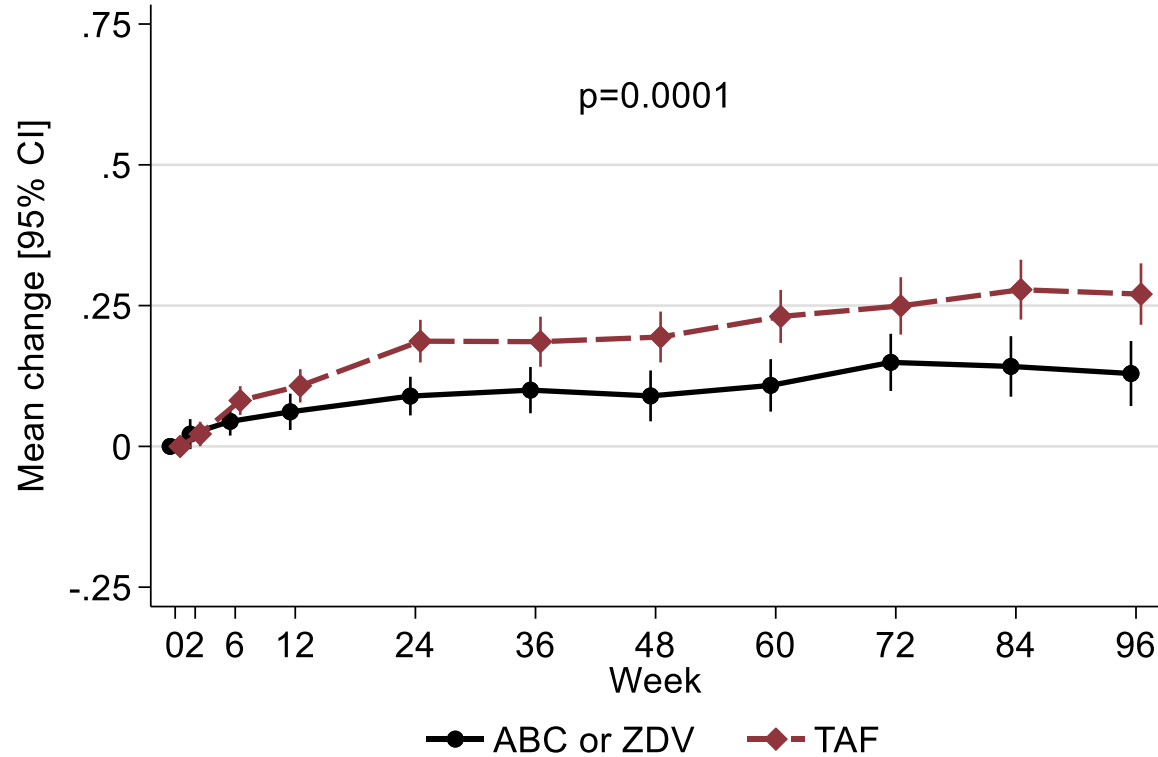


Change in Weight- and BMI-for-age Z-scores: **NRTI** backbone

- Increase in weight to week 96: +7.0kg TAF vs. +6.2 kg ABC or ZDV (SOC) (difference 0.8kg)

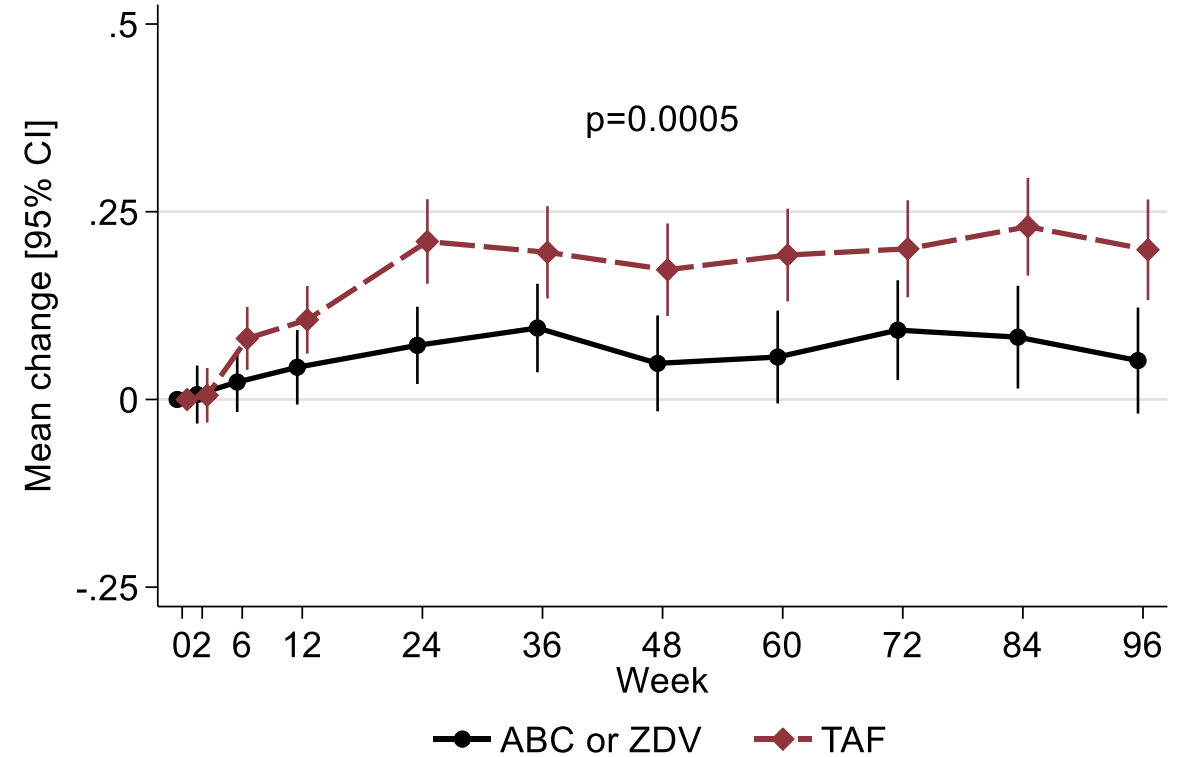
Weight-for-age

Mean change in Weight-for-age Z-score



BMI-for-age

Mean change in BMI-for-age Z-score





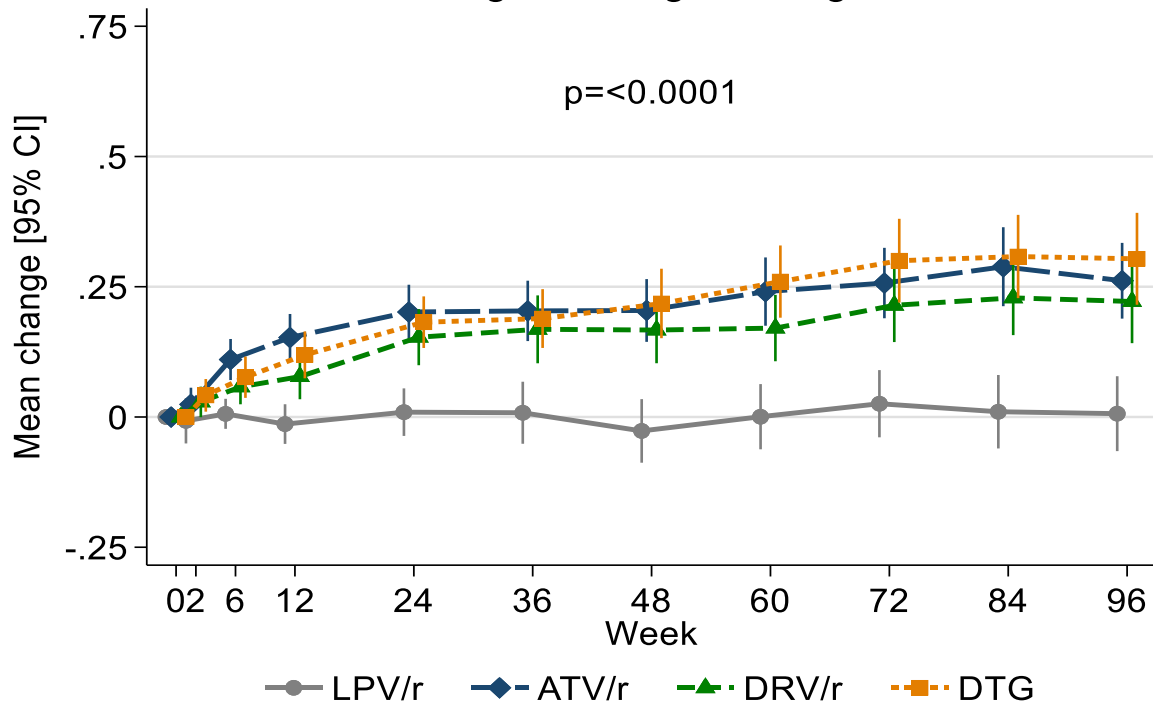
Change in Weight- and BMI-for-age Z-scores: anchor drug



- Significant increase in WAZ with all arms except LPV/r
- Change in weight to week 96: +5.6kg LPV/r vs. +6.7kg ATV/r vs. +6.7kg DRV/r vs. +7.2kg DTG

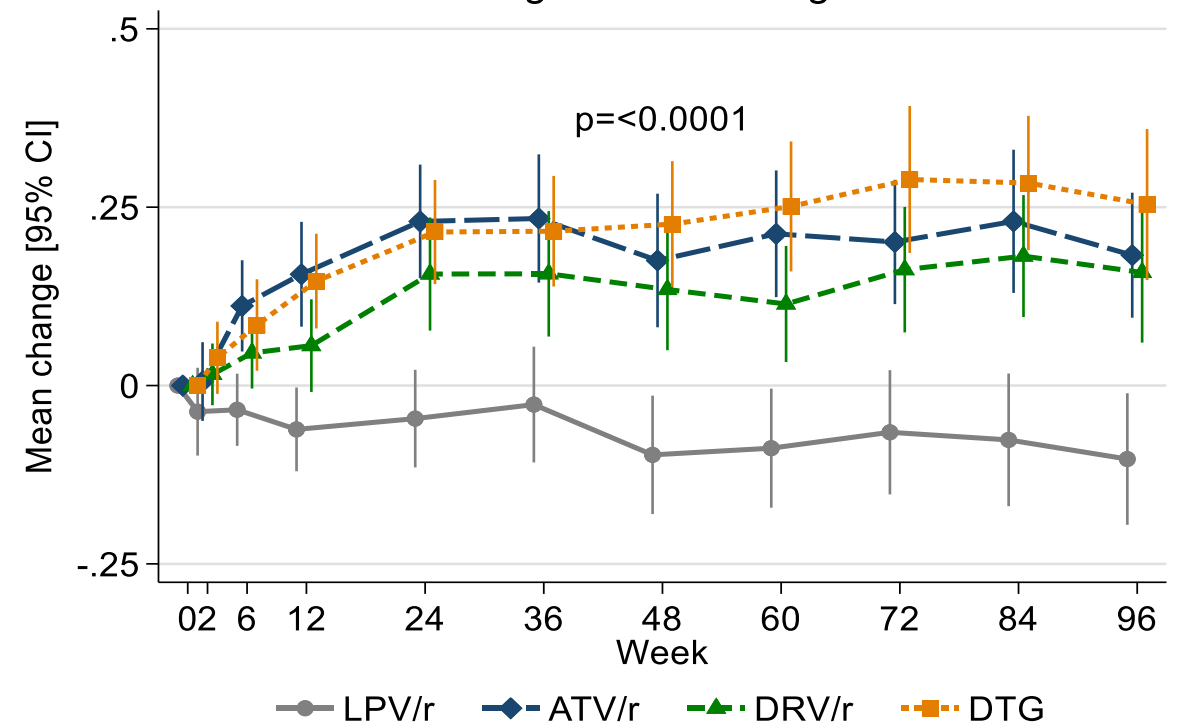
Weight-for-age

Mean change in Weight-for-age Z-score



BMI-for-age

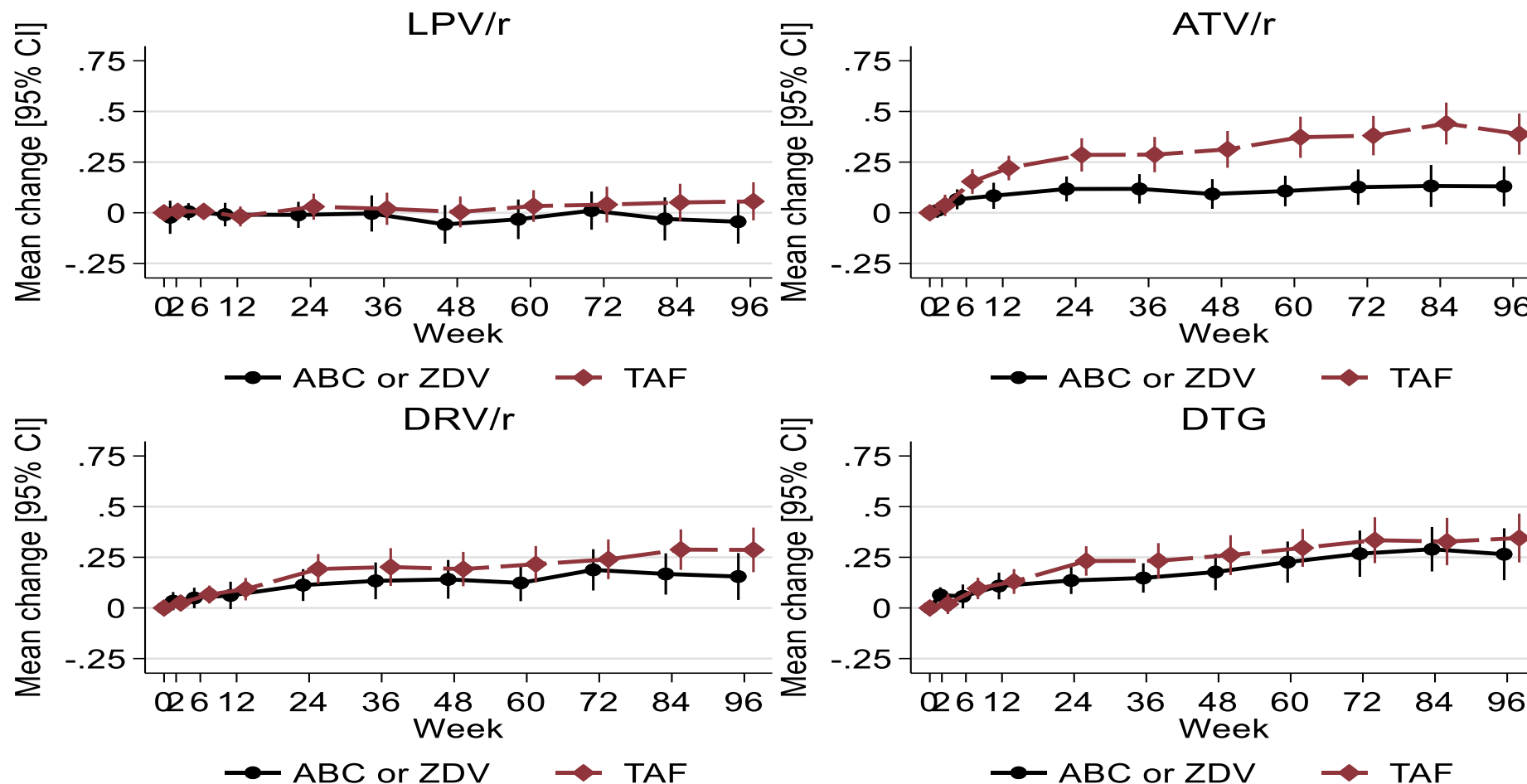
Mean change in BMI-for-age Z-score



Change in Weight-for-age: different ART combinations

- No evidence of excess weight gain among children receiving DTG and TAF (interaction $p=0.51$)

Mean change in Weight-for-age Z-score



Conclusions

- **TAF**-based regimens were superior to standard of care (ABC or ZDV)
- **DTG**-based regimens were superior to standard second-line PI-based regimens with a favourable safety profile.
- **ATV/r**-based regimens were as good as **LPV/r**-based regimens
- **DRV/r**-based regimens were as good as, and also showed a trend towards being superior to other PI-based (**ATV/r & LPV/r**) regimens.
- Children on **LPV/r** had the poorest weight gain and least favourable lipid profiles.
- Child-friendly fixed-dose combinations of **TAF/FTC** (+**DTG** or **DRV/r** or **ATV/r**) would increase access to safe and effective second-line ART options for children.



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The CHAPAS-4 study team

