Strategies for nevirapine initiation in HIV-infected children taking paediatric fixed-dose combination ‘baby pills’ in Zambia: a randomised controlled trial

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On behalf of CHAPAS-1Trial Team

CHAPAS 1 Trial

- **C**hildren with **H**IV in **A**frica – **P**harmacokinetics and **A**dherence of **S**imple Antiretroviral Regimens.

Background

- FDC scored dispersible tablets of d4T/3TC/NVP (Baby/Junior Triomune, Cipla Ltd) provide a simpler alternative to liquid formulations and have the correct dose ratios for children.
- However, to dose escalate nevirapine as recommended, separate drugs are required initially

Objective:

- To evaluate the need for dose-escalation of Nevirapine in HIV-infected Zambian children starting ART with Triomune Baby/Junior (d4T 6/12, 3TC 30/60, NVP 50/100mg**)**

Trial design & Methods

- A randomised trial of nevirapine initiation strategies in 211 ART-naïve children aged 3 months – 14 years fulfilling WHO criteria for initiating treatment
- Children were randomised to start antiretroviral therapy with:
  - dose–escalation (DE), an initial 14 days of half-dose nevirapine (Triomune am) plus Lamivir-S (combined stavudine/lamivudine) pm) followed by full-dose nevirapine (Triomune am/pm)
  - OR
  - full-dose (FD) nevirapine (Triomune am/pm)

Summary Dosing table of Pedimune (Triomune Baby/Junior)

Weight Range (kg)	Equivalent BSA range [a]	Total Tablets per day	Daily Dosing Schedule	Dose d4T (mg)	Dose 3TC (mg)	Dose NVP (mg)	Daily dose NVP[c] mg/m^2
3-<6	**0.21-0.34**	2	1 BD	12	60	100	294-476
6-<10	**0.34-0.49**	3	1½BD	18	90	150	306-441
10-<15	**0.49-0.65**	2	1 BD	24	120	200	308-408
15-<20	**0.65-0.79**	2½	1am,1½pm	30	150	250	316-385
20-<25	**0.79-0.92**	3	1½BD	36	180	300	326-380
25-<30	**0.92-1.1**	4	2 BD	48	240	400	364-435
		Daily dose of **Pedimune (Triomune) Baby (d4T 6mg, 3TC 30mg, NVP 50mg)**					
		Daily dose of **Pedimune (Triomune) Junior (d4t 12mg, 3TC 60mg, NVP 100 mg)**					

Procedures

- Seen by nurse at 2,4, weeks then 4wkly ,
  - Wgt and height, and further ART given.
  - Any adverse events or new WHO events referred to the doctor and events recorded.
- Seen by doctor at 2,4, 8, 12 weeks, then 12-weekly intervals.
  - Conducted clinical examination and recorded any new adverse events or new WHO events.
  - Blood samples for haematology, biochemistry, lymphocyte subsets and plasma storage.

Endpoints

- Primary endpoint
  - Clinical/laboratory grade 3/4 adverse events (AEs) with either a definite/probable or uncertain relationship to nevirapine

- Secondary endpoints -
  - Grade 2, 3 or 4 adverse events definitely/probably related to nevirapine

Endpoints

Secondary endpoints:

disease progression measured

-mortality

-new WHO stage 3 or 4 events

- growth and CD4 change from baseline

- All WHO 3/4 events, deaths and grade 3/4 adverse events were reviewed without knowledge of randomised group by an endpoint review committee

AEs relationship to nevirapine

- All adverse events were assessed for relationship to nevirapine
- 3 categories
  - Unrelated/unlikely related to nevirapine
  - Uncertain whether related to nevirapine
  - Definitely/probably related to nevirapine

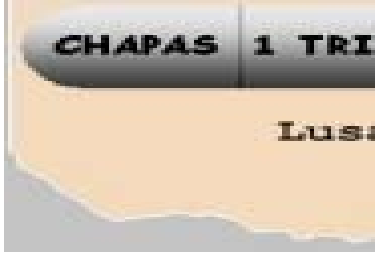
Baseline characteristics

	Dose escaclation	Full dose	All
	N=106	N=105	N=211
Sex, male, n (%)	55 (52)		
Age, years 0-2, n (%) 3-6 7-14	5.7 (2.2, 8.7) 34 (32%) 33 (31%) 39 (36%)	5.2 (1.6, 9.5) 40 (38%) 26 (25%) 39 (37%)	5.6 (2.0, 9.0) 74 (35%) 59 (28%) 78 (37%)
Weight-for-age Z score* Height-for-age Z score*	-3.0 (-4.2,-2.1) -3.1 (-4.1,-2.0)	-3.3 (-4.3,-2.2) -3.1 (-4.2,-2.4)	-3.2 (-4.3,-2.1) -3.1 (-4.1,-2.2)
WHO HIV stage n (%) 1 or 2, 3 4	 0 (0%) 68 (64%) 38 (36%)	 2 (2%) 68 (65%) 35 (33%)	 2 (2%) 136 (64%) 73 (35%)
CD4% Median (IQR)	12 (8, 8)	13 (9, 8)	13 (8, 8)

Baseline characteristics

	Dose escalation	Full dose	All
	n=106	n=105	n=211
CD4 cells/mm^3 median (IQR) 0-2 years 3-6 years 7-14 years	437 (245,797) 882 422 305	452 (231,824) 753 557 227	441 (235,819) 824 528 253
Follow-up, weeks Lost to follow-up, n (%)	96 (68,116) 8 (8%)	90 (68,113) 9 (9%)	92 (68,116) 17 (8%)

Outcomes



	DE	FD		
	n=106	n=105	RR (95%CI)	p-value
Primary endpoint: Grade 3 or 4 AEs definitely, probably or uncertainly related to NVP				
Number of events (children)	29 (24)	31 (25)		
Rate (per 100 child years)	16.5	18.0		
Rate ratio			1.1 (0.63, 1.9)	0.7
Type of event -				
Biochemical	29	30		
Haematological	0	1		

Outcomes

	DE	FD		
	n=106	n=105	RR (95%CI)	p-value
Secondary endpoint: Grade 2, 3 or 4 AEs definitely or probably related to NVP				
Number of events (children)	14 (12)	26 (22)		
Rate (per 100 child years)	8.0	15.0		
Rate ratio			1.9 (0.95,3.9)	0.05
Type of event -				
Biochemical	12	14		
Haematological	2	12		

Grade 2,3 4 AEs

- 40 Grade 2,3 4 AEs definitely probably related to nevirapine
- Nevirapine treatment unchanged by the raised LFTs, but interrupted or substituted for 13 of the 14 skin rashes, which occurred a median of 17 days after starting ART (range 8-34 days).

Nevirapine interruptions/substitutions

	Dose escalation	Full dose	Total
No of children	106 (100%)	105	211
At least 1 change off Triomune B/J	9 (8%)	19 (18%)	28 (13%)
Total changes	9	24	33
Type of change			
NVP – EFZ	5†	9†	14
NVP- ABC	1	1	2
Temporary	3	14	17
Reasons			
On ATT	5	8	13
AEs	2*	**12	14
Others	2	4	6
Total child years at risk	175.9	172.8	348.7
Rate (per 100child yrs)	5.1	13.9	9.5

Nevirapine interruptions/substitutions

- FD :DE in nevirapine interruptions/substitutions
  - IRR 2.71 95% CI [1.22,6.64] p 0.01
- NVP skin rashes: 2 (2%) DE vs 12 (11%) FD had grade 2 skin rash
- Predictors of nevirapine rash or grade 3/4 raised transaminases
  - female (OR=1.5 p=0.41), older age (OR=1.09 per year; p=0.14), higher CD4-for-age (OR=1.06 per unit z-score, p=0.38) . Non significant

Disease progression

- 22 children died (10 DE, 12 FD), 12 deaths in first 12 weeks
  - –The majority of deaths -primarily HIV related and none considered drug related. Mortality rate 6.9 and 5.7 deaths per 100 child-years in the FD and DE arms respectively (HR FD:DE=1.2 (95% CI 0.51-2.7, p=0.69).

- New/recurrent WHO events: 24 in 21 children (9DEvs 12 FD)
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	DE	FD	TOTAL
–WHO 3	7	12	19
–WHO 4	2	3	5

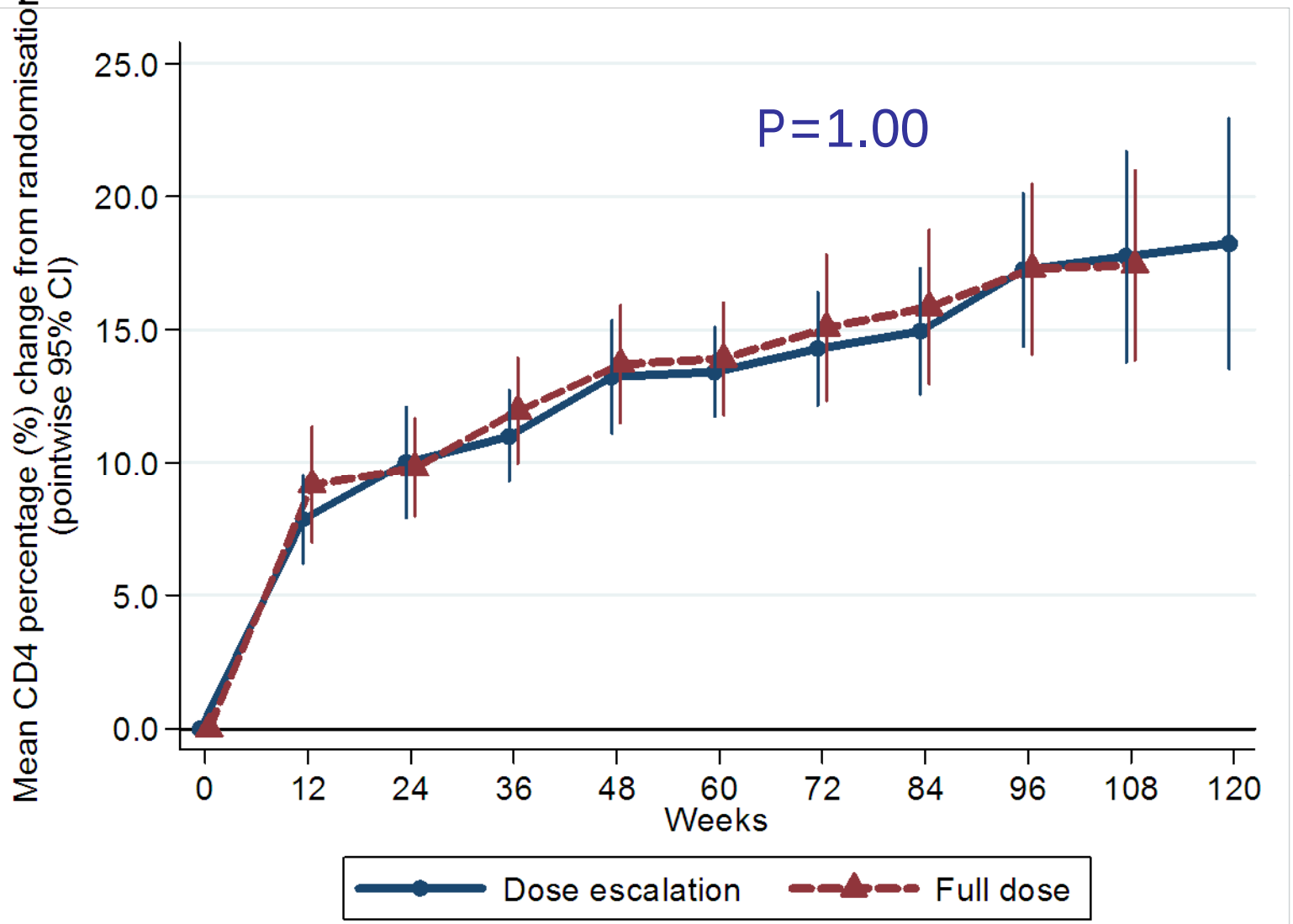
40 children had a WHO 3/4 event and/or died: 11.1 and 13.9 events per 100 child years in the DE and FD arms respectively (p=0.5)

Changes in weight, height and CD4

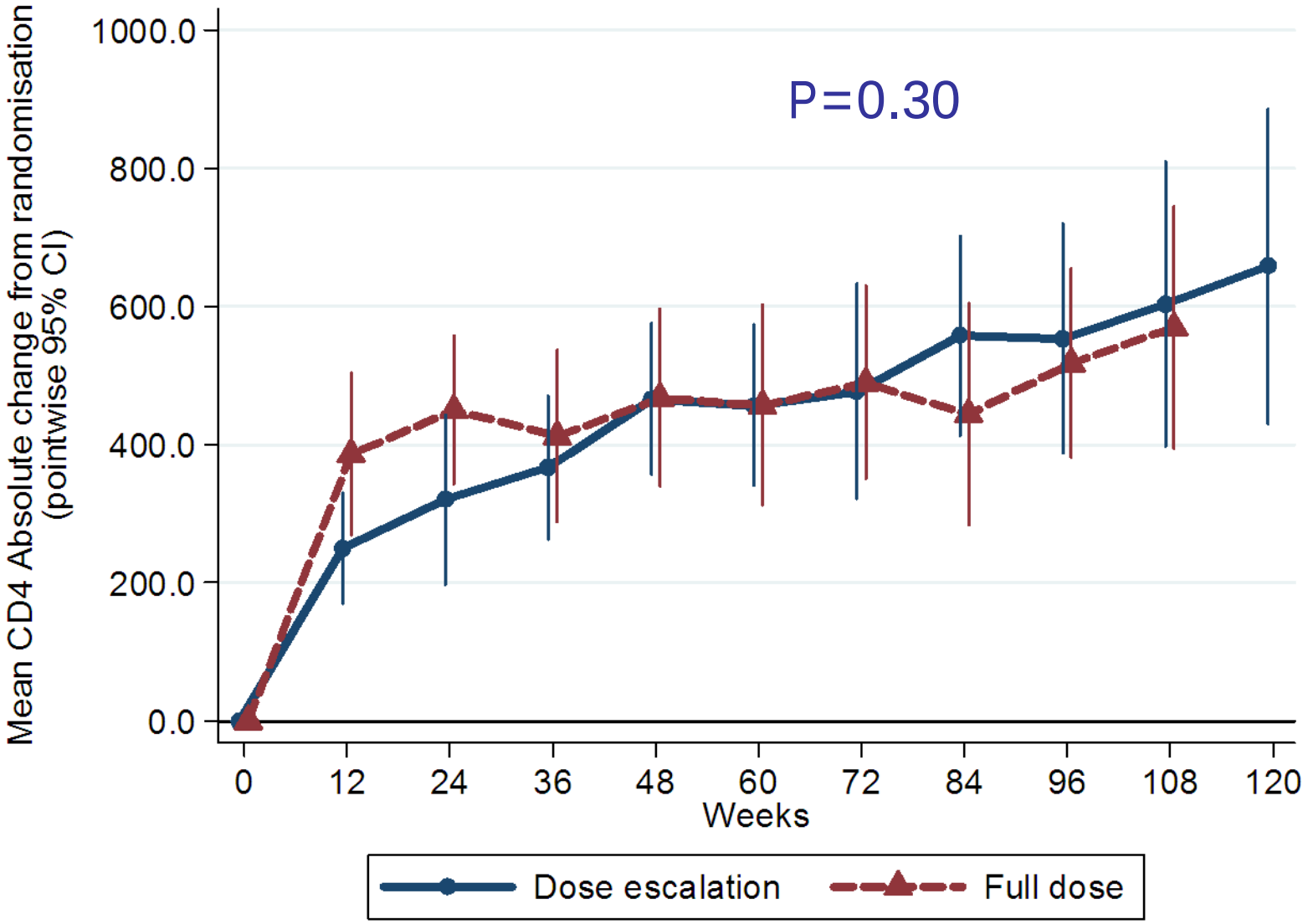
- No statistically significant differences between groups in the change in weight, height, absolute CD4 or CD4% over 96 weeks of follow-up
- Wgt for age - average 1.7 and 1.4 in FD and DE (GEE p=0.06).
- Height-for-age 0.9 and 0.7 in FD and DE (p=0.66).

- CD4 counts increase by 518 and 554, (p=0.16)
- CD4% increase by 17.3% and 17.3%, in FD and DE (p=0.99).

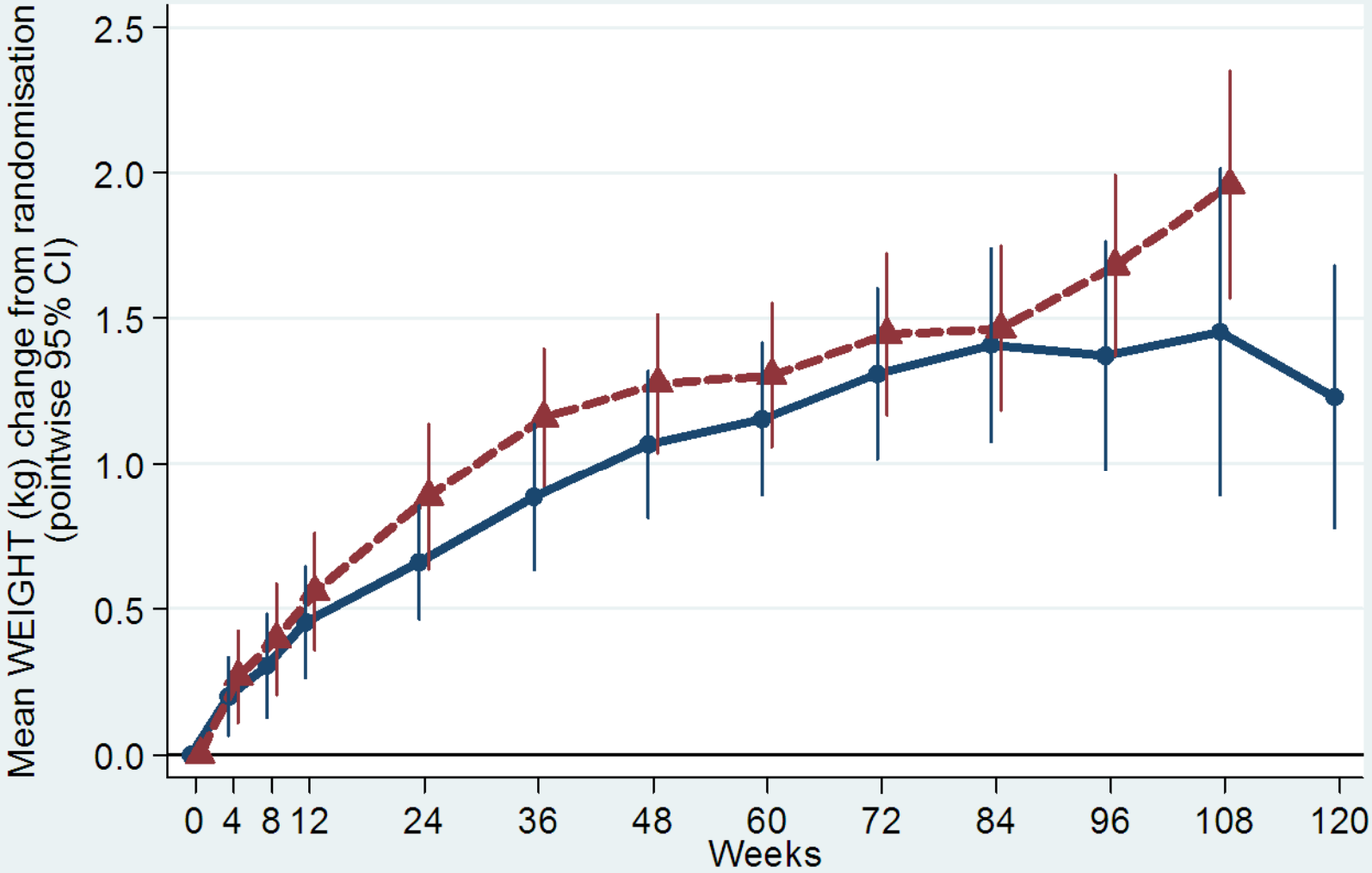
Change in CD4%



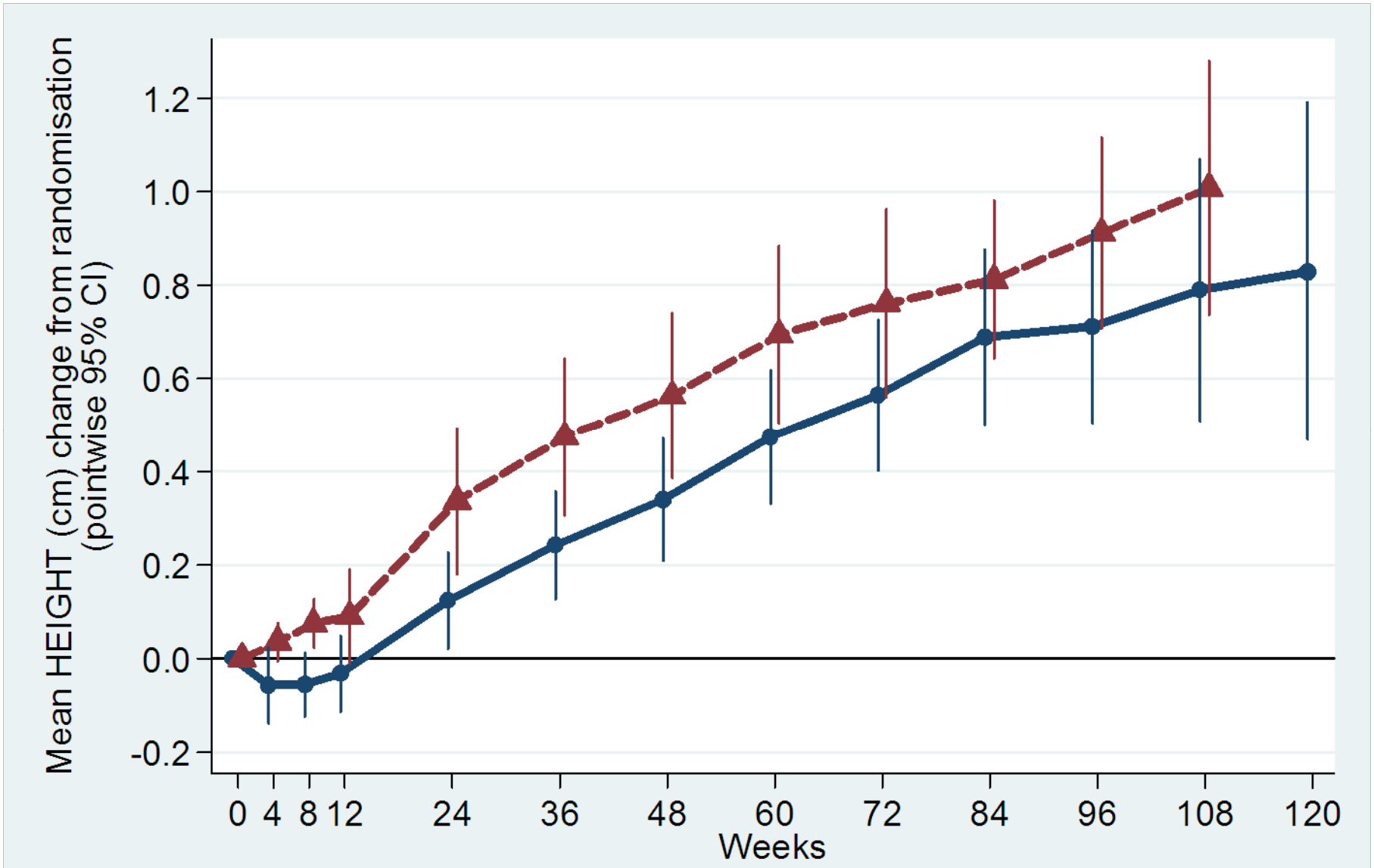
Change in CD4



Mean change in WFA z-score



Mean change in HFA z -score



Summary

- **There was no difference in grade 3/4 adverse events between the two randomised groups. None of grade 3/4 AEs were clinical.**
- **10% of children experienced NVP skin rash – Grade 2 only**
- **There were 33 nevirapine interruptions, but majority of children who temporarily stopped nevirapine due to rash were restarted on escalating dose.**

Conclusion

- **90% children who started full-dose nevirapine continued uninterrupted**
- **Although more reactions occurred when initiated at full dose than with dose-escalation, rashes were mild (grade 1 or 2), and nevirapine was successfully re-started in the majority.**
- **Evaluation of policy implications for dose-escalation of nevirapine in fixed-dose combination ART is ongoing**
  - **Dose escalation requires separate drug formulations be provided, which is complex for ART service delivery**

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