Prospective study of Lopinavir based ART for HIV Infected ChildreN Globally (LIVING study): Interim 48-week effectiveness and safety results.

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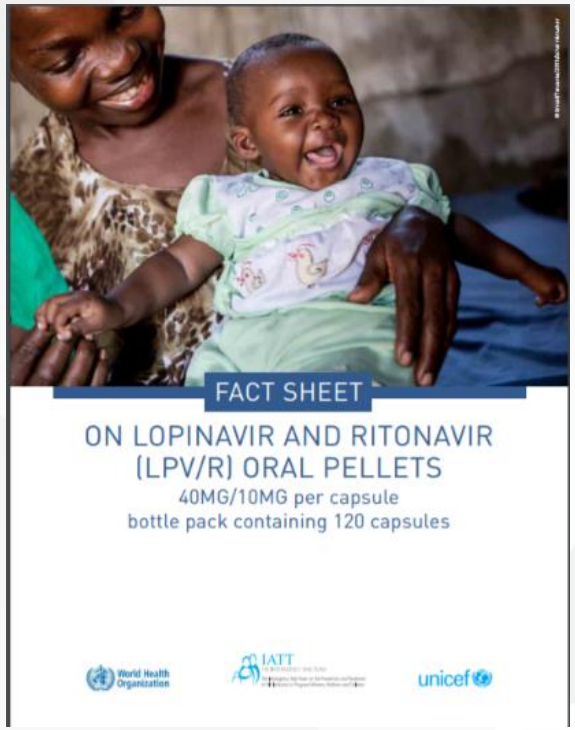
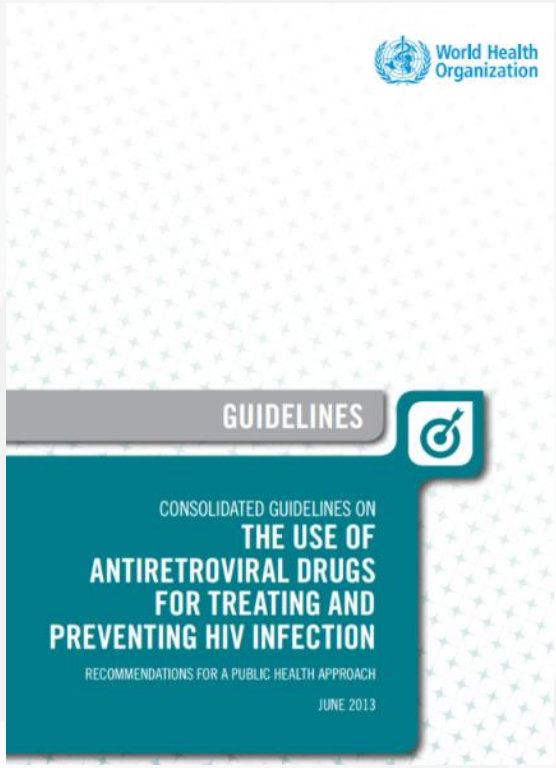
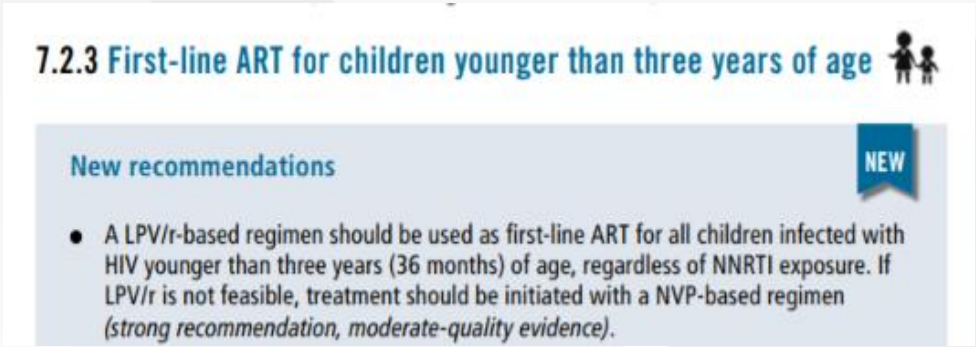
Guidelines have recommended LPV/r based first line ART for children< 3 yrs based on its superior efficacy(1)







1. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012;366(25):2380-2389. doi:10.1056/NEJMoa1113249.

Challenges with current LPV/r formulations

- **SYRUP:** contains 42% ethanol and 15% propylene glycol and
- has an unpleasant taste.
- It is NOT heat stable and requires cold chain transport.
- should be kept at 2° C-8° C at least point of dispensing.
- Once dispensed and outside the r LPV/r oral liquid is stable at 25° C f (6 weeks). LPV/r oral liquid should with food.

- **TABLET**: MUST be swallowed whole and MUST NOT be broken, crushed, chewed or dissolved before administration.
- LPV/r tablets can be taken with or without food and are suitable for children > 10kg who are able to swallow tablets whole.
- ts are NOT suitable for infants or dren that are unable to swallow e.

There is an urgent need to develop new formulations of LPV/r that are suitable for infants and young children

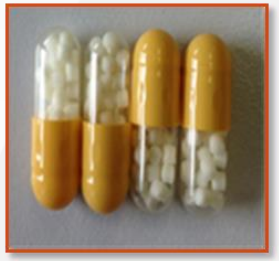
LPV/r Pellets

- Pellets are palatable, heat-stable and easy-to-administer.
- Received tentative approval by USFDA in 2015 for use infants and young children.
- However, there is little clinical data on effectiveness and safety in routine care.

LPV/r Pellets

LIVING study Objective

To evaluate the effectiveness, safety, pharmacokinetics and acceptability of LPV/r pellets with ABC/3TC (or AZT/3TC) dispersible tablets under field conditions in HIV infected infants and young children who cannot swallow tablets.



LPV/r pellets

+

NRTI tablets

Study design

- Single arm phase IIIb study.
- open-label
- Prospective
- non-randomized
- non-comparative
- multicenter, multi-country

LIVING study: Inclusion criteria

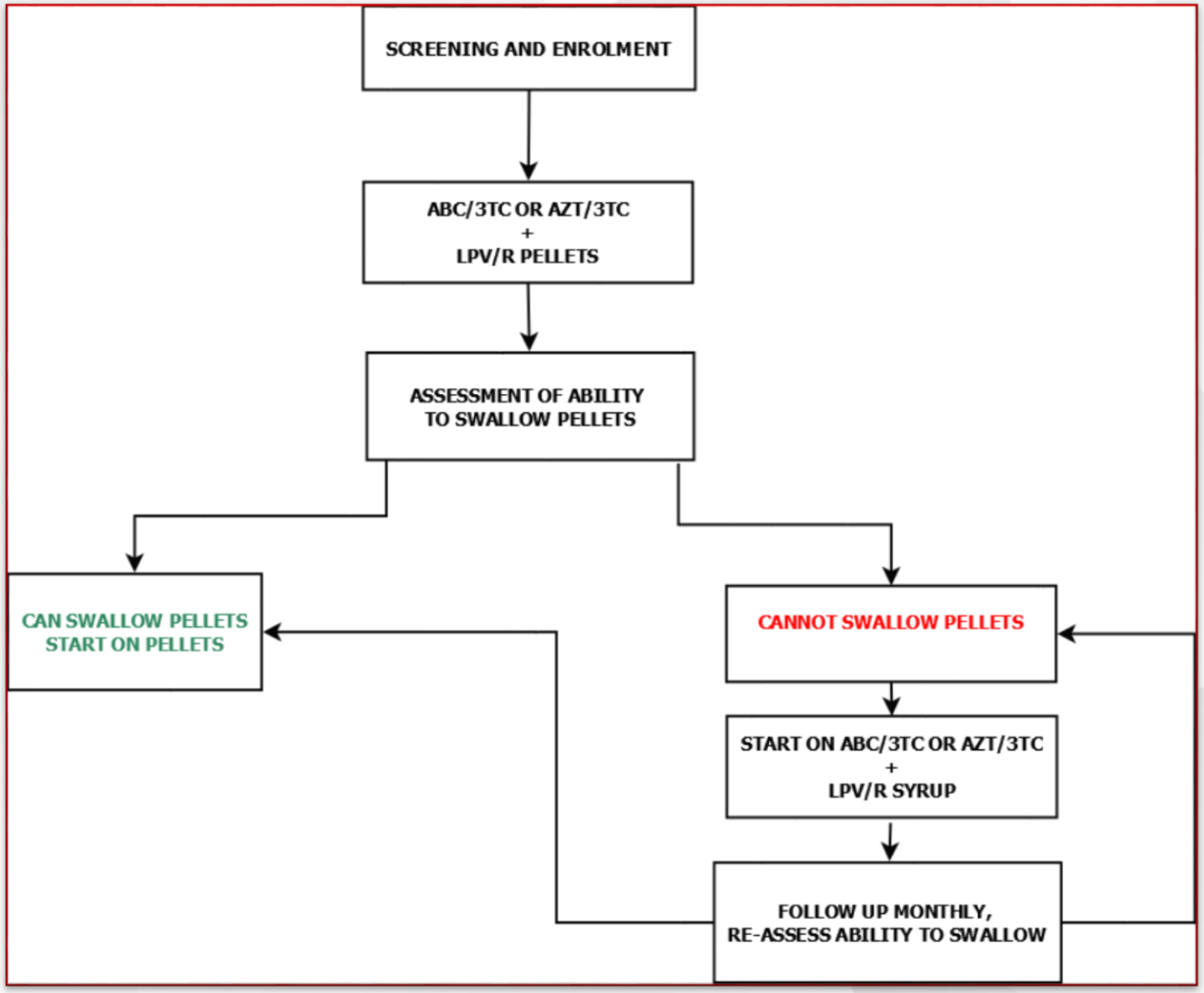
HIV-1 infected children:

1. Weight ≥3 and <25 kg at the time of enrolment. (Age is not an inclusion criterion)
2. ARV naïve, or already on first line liquid lopinavir based treatment, or Failing first line NNRTI based therapy.
3. Unable to swallow tablets

LIVING study : Exclusion criteria

- Planned or concurrent use of NNRTIs, integrase inhibitors, entry inhibitors, or PIs other than LPV/r.
- PIs treatment failure with the presence or strong suspicion of a PI resistance mutation.
- Current treatment with a drug that interacts significantly with LPV/r.
- Any clinically significant disease in the investigator's opinion, would compromise participation in this study.
- Contraindications to PI use.
- Treatment with experimental drugs for any indication within 30 days prior to study entry.
- Anticipated transfer to non study treatment site.

LIVING study : Screening and enrolment



LIVING study :TEST DRUGS

Drug	Strength of tablets (mg)	Number of tablets by weight-band morning and evening									
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg	
		am	Pm	am	pm	am	pm	Am	pm	am	pm
AZT/3TC	Tablet 60mg/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3
ABC/3TC	Tablet 60mg/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3
LPV/r	40/10 mg pellets	2	2	3	3	4	4	5	5	6	6
LPV/r	80/20mg/mL	1	1	1.5	1.5	2	2	2.5	2.5	3	3

LIVING study: Enrolment status by country (as of 31st May 2017)

Country	Site Name	Enrolled
Kenya	Kenyatta National Hospital	75
	Gertrude's children's hospital	50
	FACES, St Lumumba, Kisumu	80
	AMPATH, MRTH, Eldoret	66
	TOTAL	**271**
Uganda	JCRC – Lubowa, Kampala	30
	Epicenter - Mbarara	66
	Baylor childrens' clinic, Mulago	70
	JCRC – Port Fortal	50
	JCRC-Gulu	34
	TOTAL	**250**
GRAND TOTAL		**521**

LIVING study: Participants' Disposition.

Total enrolled (n=521)

ARV experienced **467** (NNRTI =34; NNRTI+LPV/r =433); ARV naïve =**54**

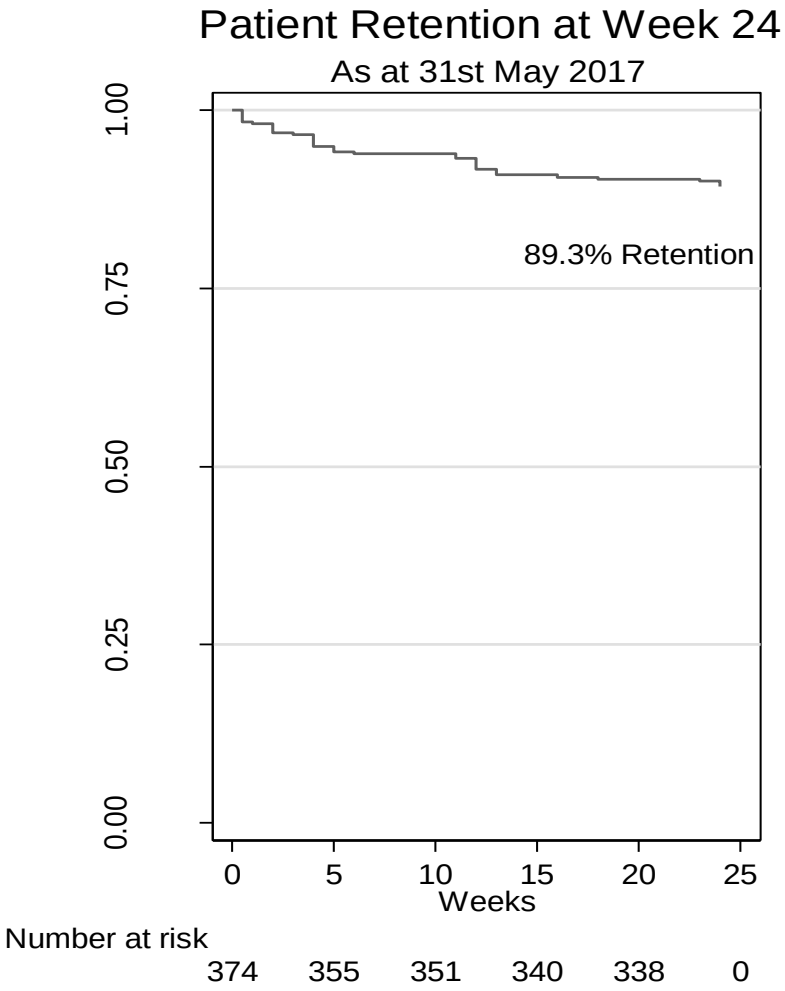
Visit Month 3 (n = 402)

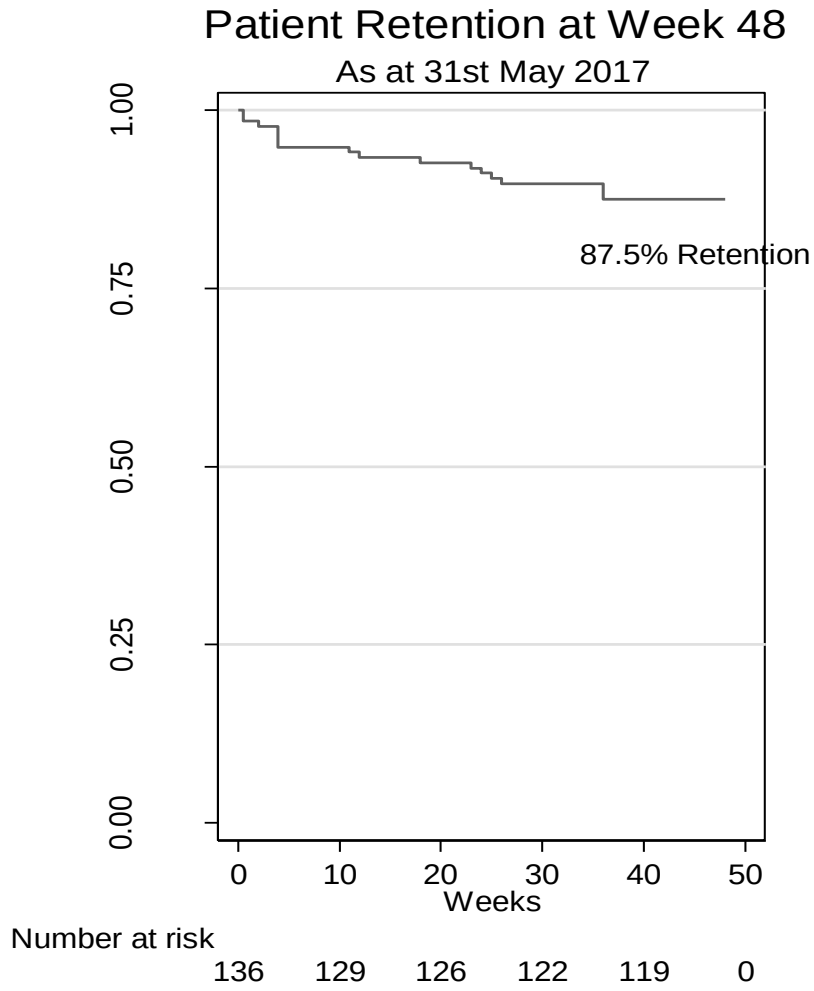
Visit Month 6 (n = 331)

Visit Month 12 (n = 119)

- **Total drop out (n=18)**
- Loss to follow-up (n=2)
- Death (n= 4)
- Withdrawal of consent (n= 9)
- Other reason (n=3)

LIVING study Patient retention: 87.5% at week 48





LIVING study: Baseline Characteristics(n=96)

	n	%
Sex		
• Male	48	50.0
• Female	48	50.0
ART regimen at enrolment		
• ART naive	5	5.2
• Prior LPV/r exposed	86	89.6
• Prior NNRTI (NVP)	5	5.2

	Naïve		Prior LPV/r		Prior NNRTI		Total	
	median	IQR	median	IQR	median	IQR	median	IQR
pre-enrolment ART duration (Months)	0	0	23.6	10.4- 47.7	22.1	11.5- 32.1	23.2	10.4-45.5

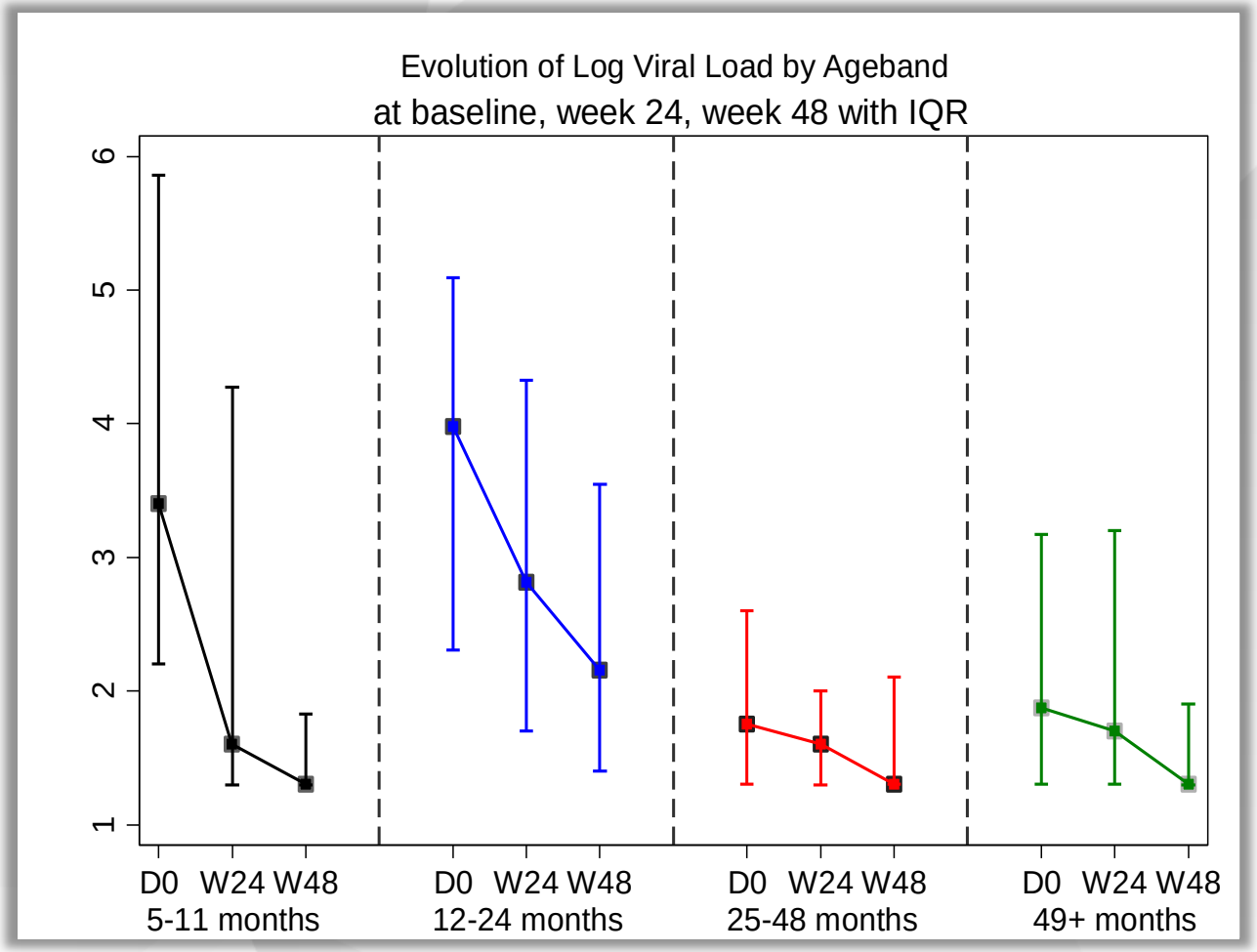
LIVING study: Baseline characteristics by ART exposure

	Naïve	LPV/r Exposed	NNRTI exposed
Median age in months (IQR)	24(14-44)	43 (26-60)	46 (41-68)
Median weight in Kg (IQR)	9 (7-11)	14 (12-16)	13.8 (11.2-15)
% with VL< 1000 copies/ml	0%	76.7%	20%
Median VL log 10 copies/ml (IQR)	5.3(4.7-5.7)	2.1 (1.6-3.9)	4.6 (4.0-5.5)
% with no immunodeficiency*	20%	58.1%	60%
pre-enrolment ART duration			

*based on WHO age-specific CD4 cut-offs

LIVING study: Viral load suppression stratified by age at enrolment

		Enrolment	Month 6	Month 12
Age group	n	Median(IQR)	Median(IQR)	Median(IQR)
5-11	8	3.4 (2.2-5.9)	1.6 (1.3-4.3)	1.3 (1.3-1.8)
12-24	13	4.0 (2.3 -5.1)	2.8 (1.7-4.3)	2.2 (1.4-3.5)
25-48	37	1.8 (1.3 -2.6)	1.6 (1.3-2.0)	1.3 (1.3 -2.1)
49+	38	1.9 (1.3 -3.2)	1.7 (1.3 -3.2)	1.3 (1.3-1.9)
Total	96	2.0 (1.3 -4.0)	1.6 (1.3-2.7)	1.3 (1.3-2.1)

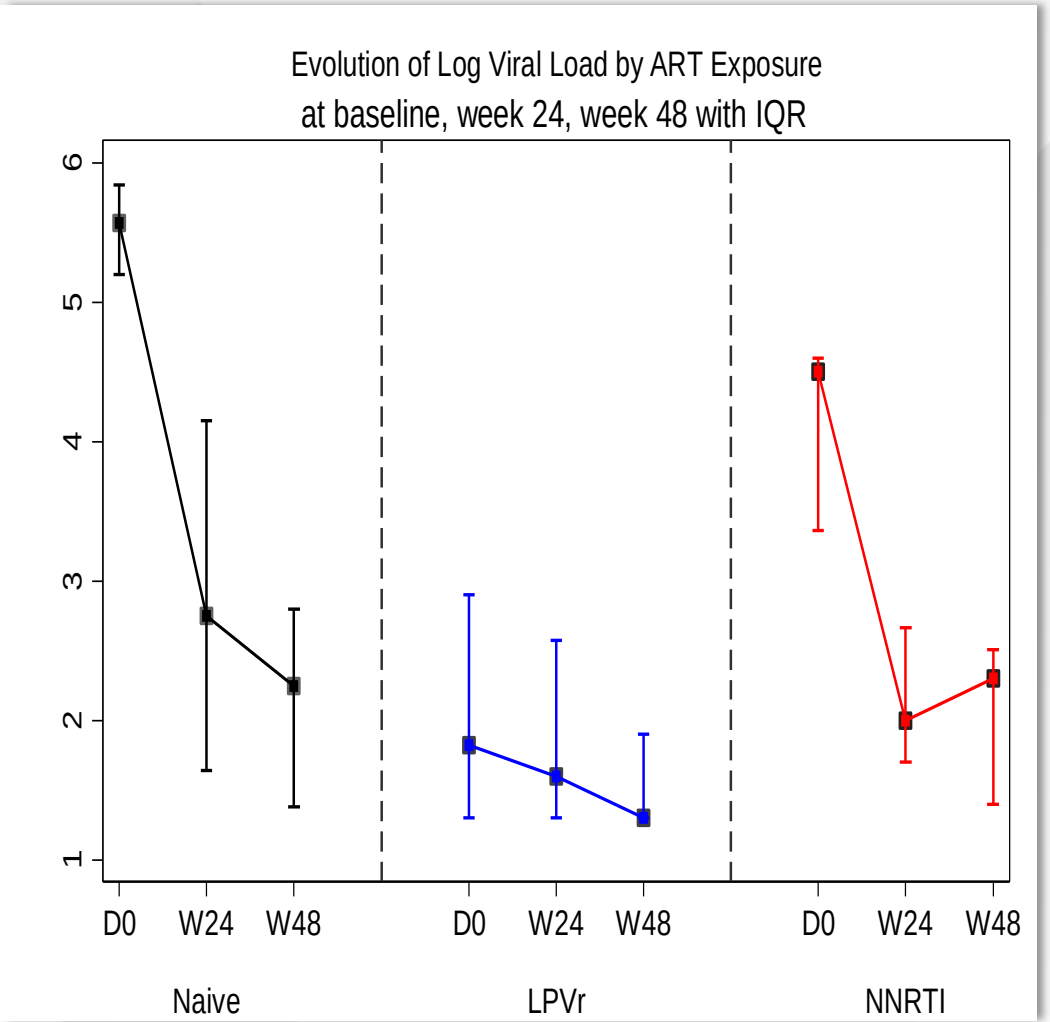


LIVING study : Evolution of Viral suppression stratified by age at enrolment

Viral load (copies/ml)	5-11 months						12-24 months						25-48 months						49+ months					
	Baseline		M6		M12		Baseline		M6		M12		Baseline		M6		M 12		Baseline		M 6		M12	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<50	2	25.0	5	62.5	6	75.0	2	15.4	3	23.1	6	46.2	17	45.9	27	73.0	26	70.3	16	42.1	19	50.0	25	65.8
<400	3	37.5	5	62.5	7	**87.5**	4	30.8	5	38.5	7	**53.8**	28	75.7	33	89.2	33	**89.2**	25	65.8	29	76.3	33	**86.8**

LIVING study: Viral load (log) suppression stratified by prior ART exposure

ART Exposure	n	Enrolment	Month 6	Month 12
		Median(IQR)	Median(IQR)	Median(IQR)
Naive	5	5.6 (5.2-5.8)	2.8 (1.6-4.2)	2.3 (1.4-2.8)
LPVr	86	1.8 (1.3-2.9)	1.6 (1.3-2.6)	1.3 (1.3-1.9)
NNRTI	5	4.5 (3.4 -4.6)	2.0 (1.7-2.7)	2.3 (1.4-2.5)
Total	96	2.0 (1.3 -4.0)	1.6 (1.3-2.7)	1.3 (1.3-2.1)

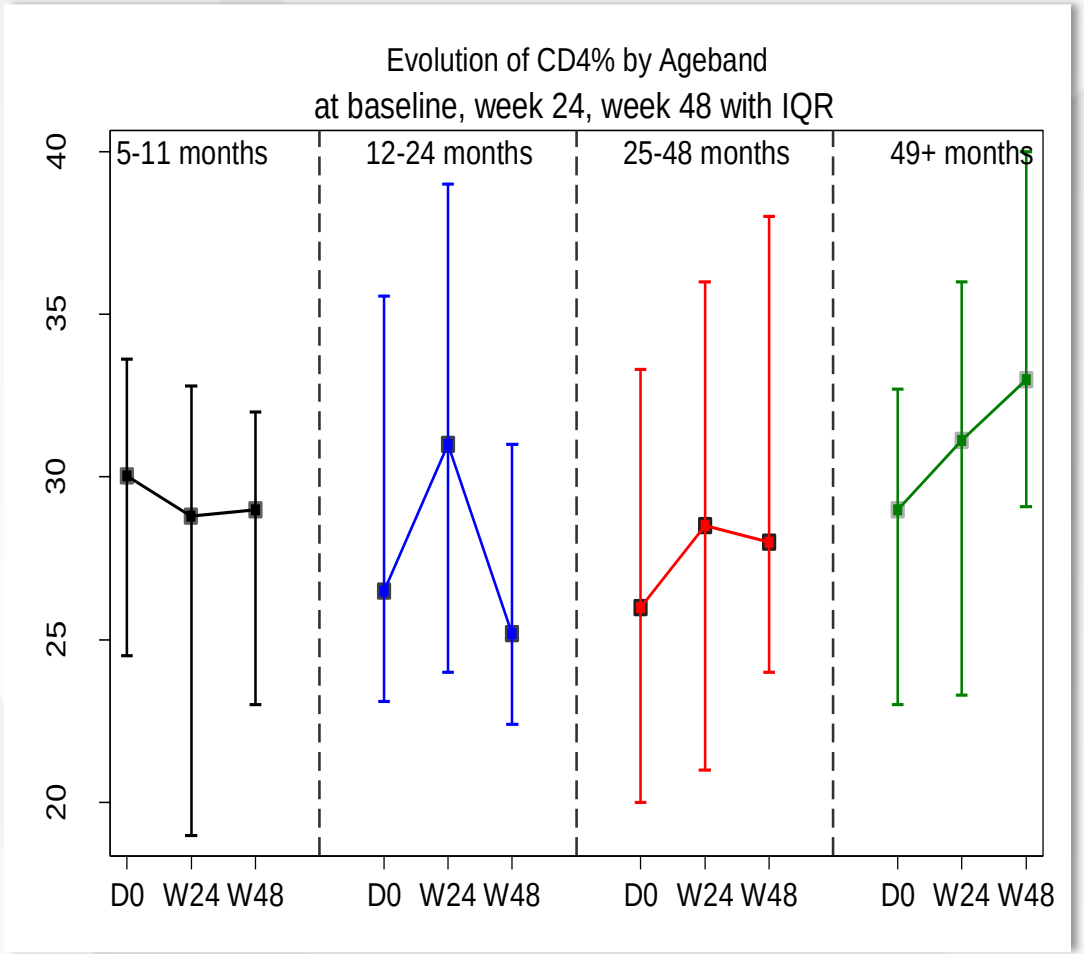


LIVING study: Evolution of Viral suppression stratified by prior treatment exposure.

Viral load (copies/ml)	naive						LPVr						NNRTI						Total					
	Baseline		M 6		M 12		Baseline		M 6		M 12		Baseline		M 6		M 12		Baseline		M 6		M 12	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<50	0	0	2	40	2	40	36	42	51	59	59	68.6	1	20	1	20	2	40	37	39	54	56	63	66
<400	0	0	3	60	3	**60**	59	69	66	77	74	**86**	1	20	3	60	4	**80**	60	63	72	75	80	**83**

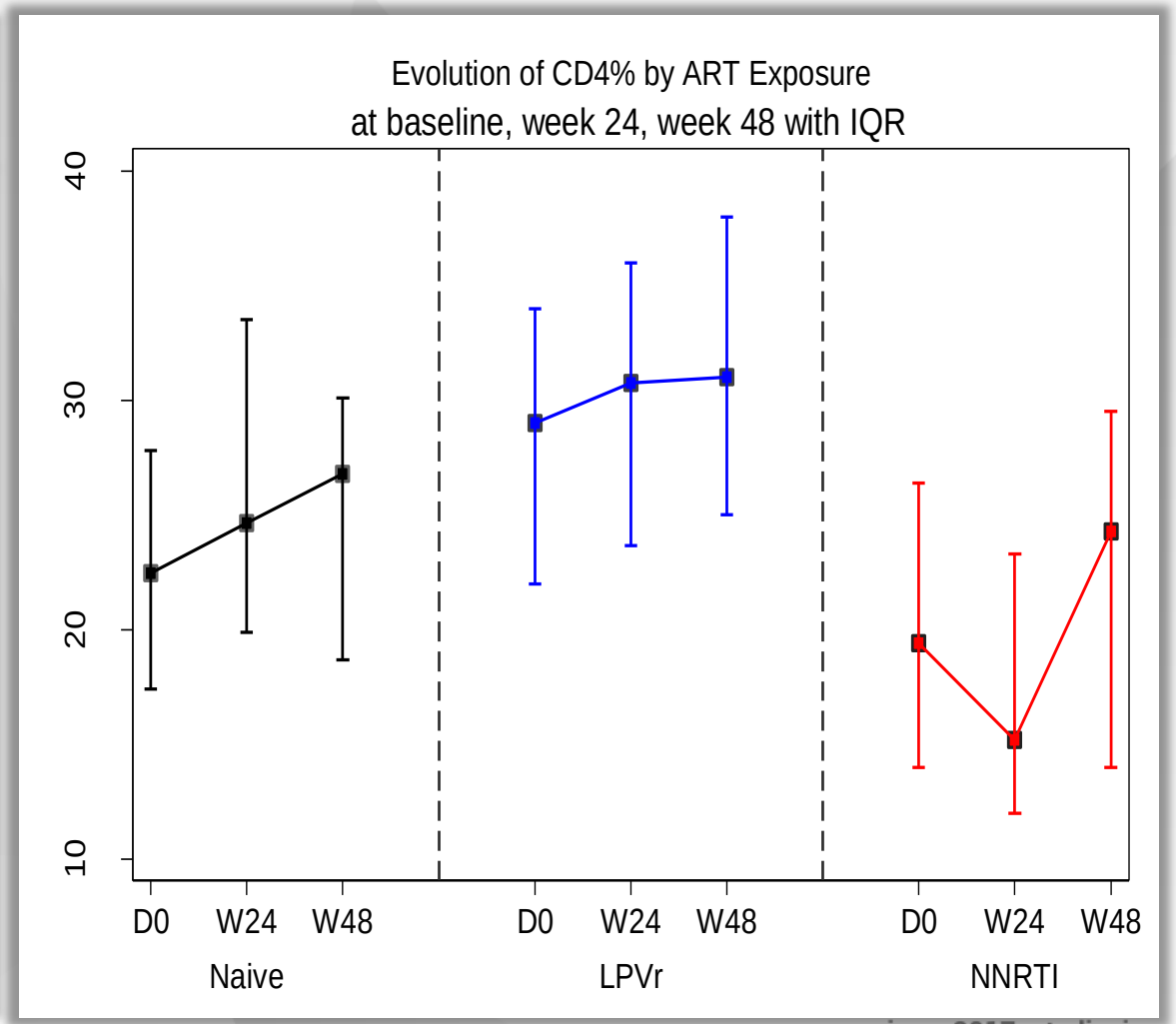
LIVING study: Evolution of immune recovery(CD4%) stratified by Age at enrolment

	n	Enrolment	Month 6	Month 12
Age group		Median(IQR)	Median(IQR)	Median(IQR)
5-11	8	30.0 (24.5-33.6)	28.8 (19.0-32.8)	29.0 (23.0-32.0)
12-24	13	26.5 (23.1-35.5)	31.0 (24.0-39.0)	25.2 (22.4-31.0)
25-48	37	26.0 (20.0-33.3)	28.5 (21.0-36.0)	28.0 (24.0-38.0)
49+	38	29.0 (23.0-32.7)	31.1 (23.3-36.0)	33.0 (29.1-40.0)
Total	96	28.4 (22.0-34.0)	29.0 (22.0-36.0)	30.1 (24.8-38.0)

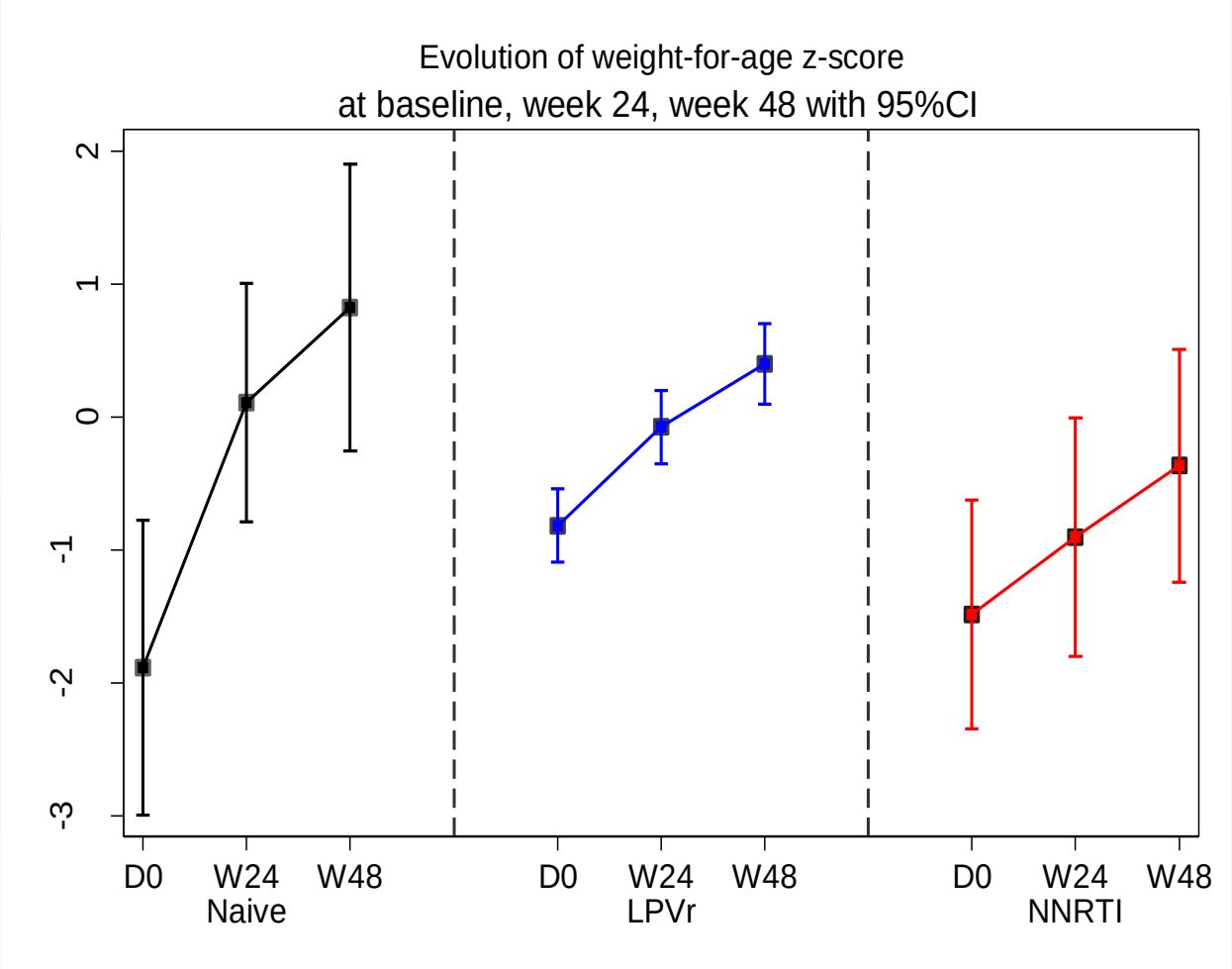


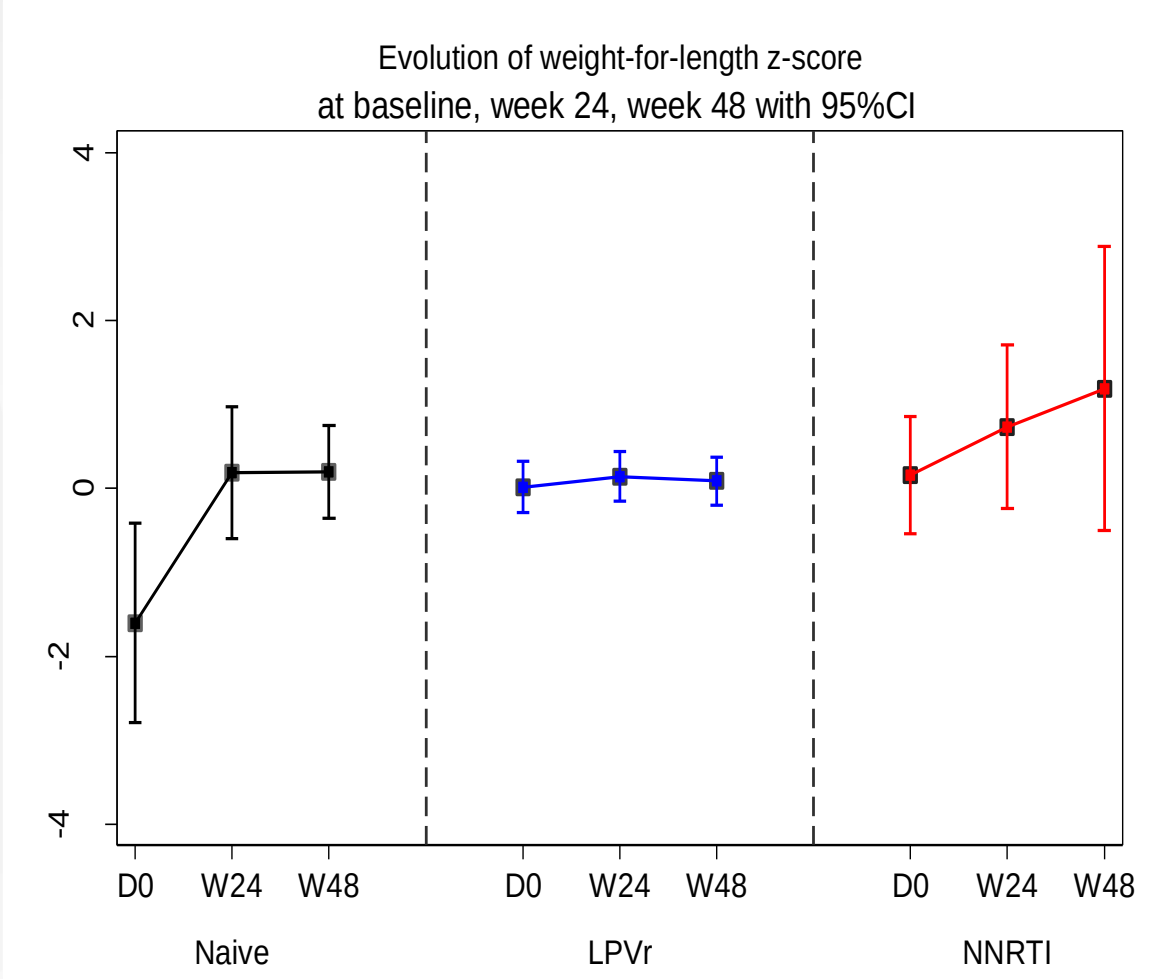
LIVING study: Evolution of immune recovery(CD4%) stratified by prior ART exposure table

	n	enrolment	Month 6	Month 12
ART Exposure		Median(IQR)	Median(IQR)	Median(IQR)
Naive	5	22.5 (17.4-27.8)	24.7 (19.9-33.5)	26.8 (18.7-30.1)
LPVr	86	29.0 (22.0-34.0)	30.7 (23.7-36.0)	31.0 (25.0-38.0)
NNRTI	5	19.4 (14.0-26.4)	15.2 (12.0-23.3)	24.3 (14.0-29.5)
Total	96	28.4 (22.0-34.0)	29.0 (22.0-36.0)	30.1 (24.8-38.0)

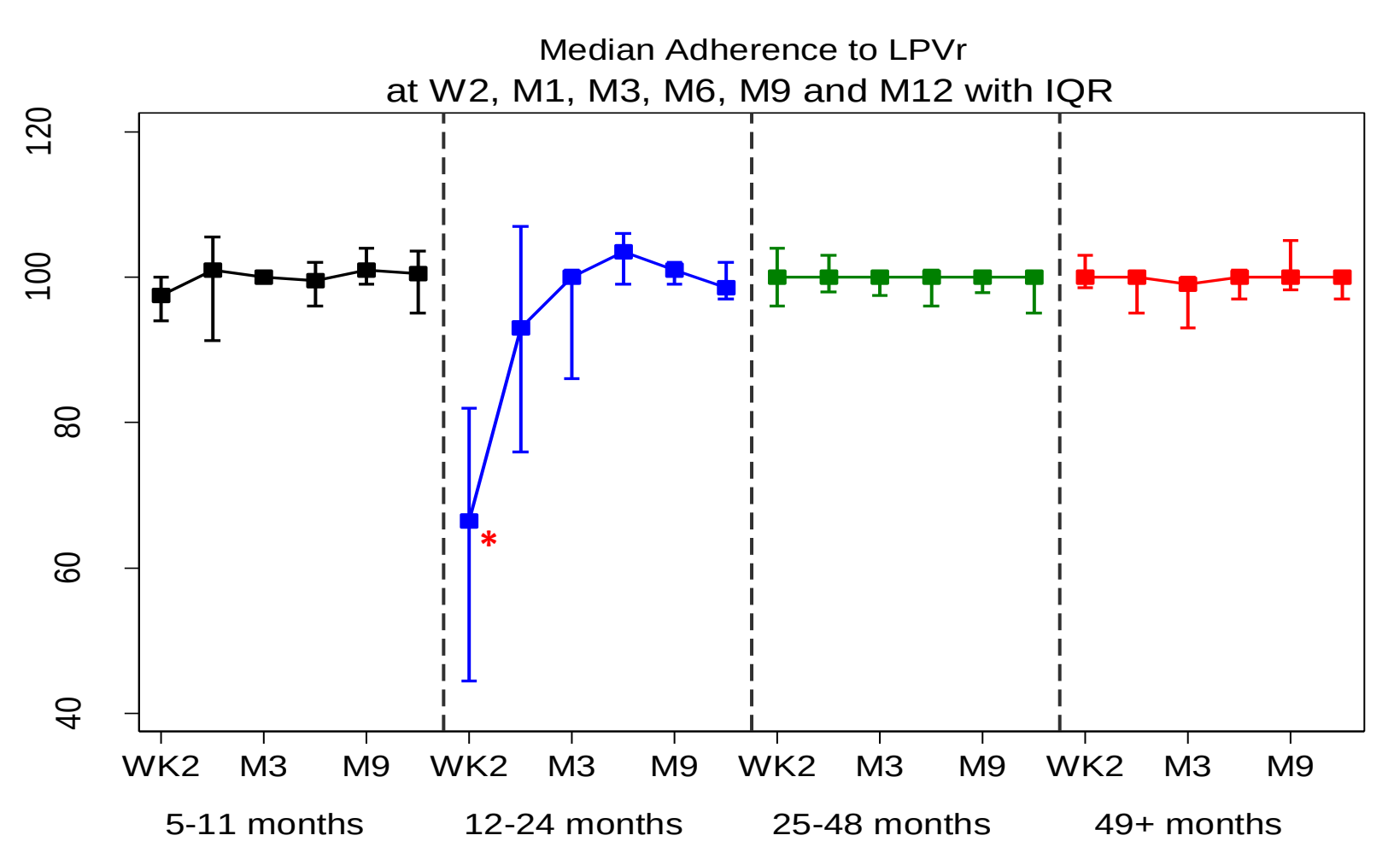


LIVING study: Evolution of anthropometric parameters stratified by prior ART exposure.





LIVING study: Calculated adherence (pill counts)



* 2 children experienced difficulties during the 1st 2 weeks and

LIVING study: Adverse events (n=96)

AE preferred term	Number of events	Number of children
	n	
UPPER RESPIRATORY TRACT INFECTION	36	24
RHINITIS	22	17
DIARRHOEA	13	11
RESPIRATORY TRACT INFECTION	11	10
OTITIS MEDIA	10	9
PHARYNGITIS	9	8
ANAEMIA	8	7
DERMATITIS	8	6
NASOPHARYNGITIS	8	6
COUGH	6	6

LIVING study : Serious adverse events (n=96 as of 31st May 2017)

SAE Description	seriousness criteria	relatedness to study medications
respiratory tract infection	hospitalization	not related
Elevated ALT	important medical event	related
severe malaria	hospitalization	Not related
Severe anemia	hospitalization	Not related

LIVING study : discussion

Trial name	Treatment regimen	Number of subjects	VL < 400copies/ml 6 months (24 weeks)	VL < 400copies/ml 12 months (48 weeks)
Ph I/II LPV/r in infants 6 weeks-6 months (P1030)	LPV/r + 2 NRTIs	21	48%	
ARV for children with peripartum NVP exposure (P1060)	LPV/r + AZT +3TC	63 (<12months)	76.7%*	
	LPV/r + AZT +3TC	19(>12months)	82.5%*	
NVP vs LPV/r for HIV infected children (no prior NVP exposure P1060)	LPV/r + AZT +3TC	36 (<12months)	80.6%*	
	LPV/r + AZT +3TC	104(>12months)	80.8%*	
	LPV/r + AZT +3TC	140 (combined)	80.7%*	
CHER	LPV/r + AZT + 3TC or second line with ddI + ABC + NVP or EFV	125 (ART-Deferred)	87%	
		126 (ART-40 weeks)	84%	
		126 (ART- 96 weeks)	83%	
LIVING (interim results 2017)	LPV/r +ABC/3TC or AZT/3TC	96 (all cohorts combined)	**75.1%**	**83%**

LIVING study : Conclusion

- Treatment with LPV/r based ART is associated with satisfactory levels of viral suppression regardless of prior ART regimen.
- Good CD4 reconstitution and anthropometric improvements.
- The LPV/r pellets based therapy has been effective and well tolerated, with minimal safety concerns.

Next steps

- Complete LIVING study in 2018.
  - Complete recruitment in Tanzania
  - Sparse PK data analysis
  - Analyze HIVDRT in children who remain viremic at M6 and M12
- Work with stakeholders to improve access to LPV/r pellets within national paediatric HIV treatment programs (important to streamline drug orders)

Acknowledgements

- We thank children and caregivers who participated in the study.
- All LIVING study site staff.
- DNDi staff in Nairobi and Geneva
- Ministry of Health in Kenya and Uganda

Acknowledgement

This study has been made possible through Unitaid's support

Additional Funders

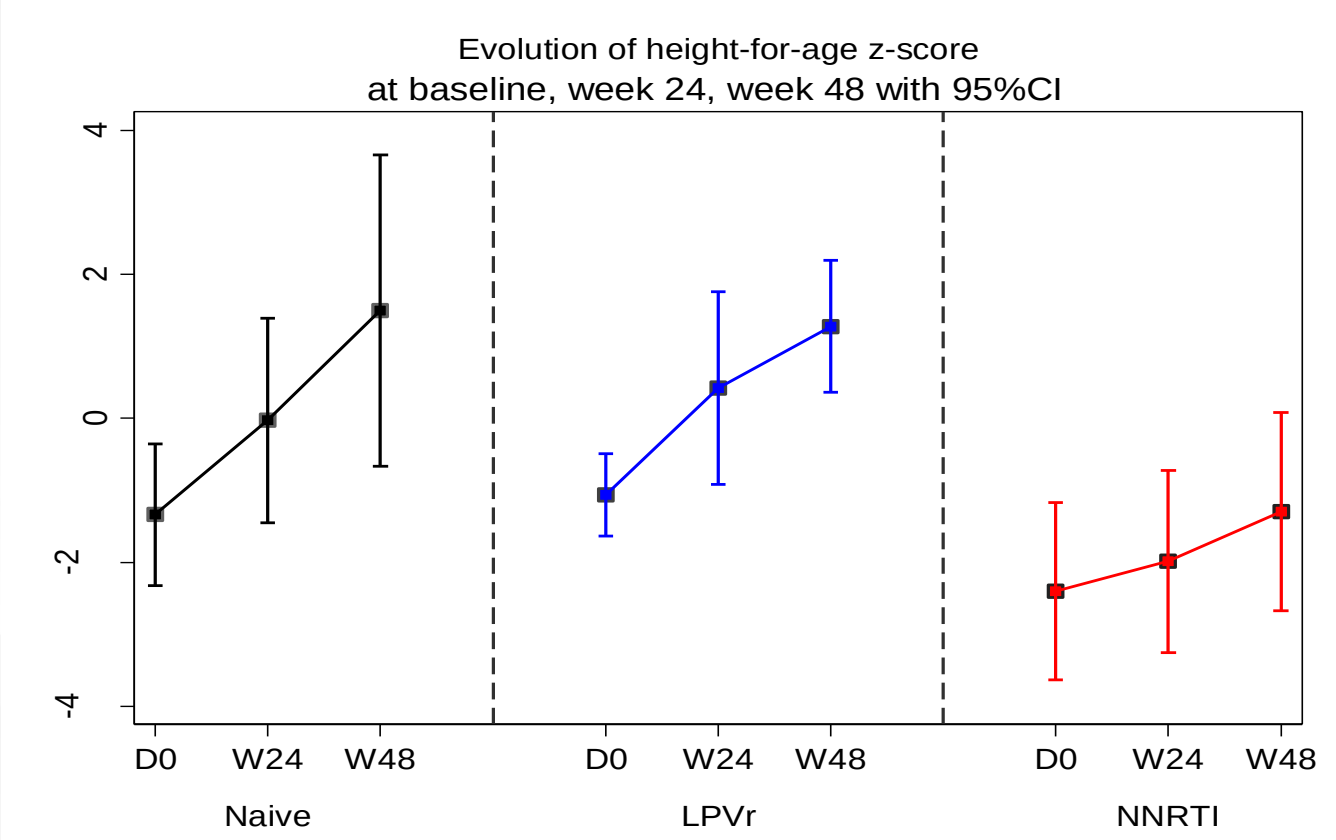
Partners

DNDi

Drugs for Neglected Diseases *initiative*

Thank you very much,
Merci beaucoup.

Back up slide -1



Additional slide -2 Evolution of Viral suppression.

Timepoint	VL (copies/ml)	ART naive		NNRTI+LPV/r		NNRTI	
		n	%	n	%	n	%
	≥1000	5	100	20	23.3	4	80
baseline	<1000	0	0	66	76.7	1	20
	≥1000	2	40	16	18.6	1	20
week 24	<1000	3	60	70	81.4	4	80
	≥1000	2	40	10	11.6	1	20
week 48	<1000	3	60	76	88.4	4	80

Immune reconstitution: gain in CD4+ T cells by prior ART exposure

	ART naive		LPV/r		NNRTI		Total	
	n	%	n	%	n	%	n	%
Baseline								
None	1	20	50	58.1	3	60	54	56.3
Immunodeficiency	4	80	36	41.9	2	40	42	43.8
Week 24								
None	1	20	54	62.8	2	40	57	59.4
Immunodeficiency	4	80	32	37.2	3	60	39	40.6
Week 48								
None	2	40	55	64	2	40	59	61.5
Immunodeficiency	3	60	31	36	3	60	37	38.5