OPTIMISING FORMULATIONS

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Skills Building Session: Infant testing

Background[1]

- Of the children living with HIV globally (most in Africa), only 43% are receiving antiretroviral therapy (ART), many with suboptimal formulations.

- **Formulation shortfalls** pose a series of challenges to meeting global treatment targets:
  - 1·6 million children (aged 0–14 years) on ART by the end of 2018 (95% coverage)
  - ensuring that 95% of those on ART are virologically suppressed.

[1] Penazzato M et al; Catalysing the development and introduction of paediatric drug formulations for children living with HIV: a new global collaborative framework for action. *The Lancet HIV*, Vol.5; Issue 5; Pe259-e264, May 01, 2018

NATIONAL CONSOLIDATED GUIDELINES

FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV (PMTCT) AND THE MANAGEMENT OF HIV IN CHILDREN, ADOLESCENTS AND ADULTS

First-line regimens for ART initiation in children:

Children <3 years or older children weighing <10kg

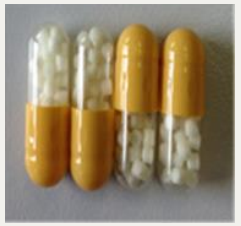
Regimen = ABC + 3TC + LPV/r

Heavy to carry, hard to hide, difficult to dose, cold chain requirements, bitter taste….

Progress to develop child-friendly solid formulations and in fixed-dose combinations

Lopinavir / ritonavir paed tablets 100mg / 25mg: Abbvie, Hetero and McLeods – tentative FDA approval (PEPFAR) in 2016

Abacavir and Lamivudine Tablets for Oral Suspension 60 mg / 30 mg and 120mg / 60 mg: Mylan and Cipla – tentative FDA approval (PEPFAR) in 2014 and 2017



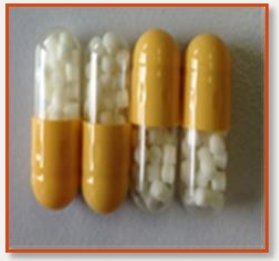
Lopinavir / ritonavir pellets or granules 40mg / 10mg: Cipla and Mylan - tentative US FDA approval (PEPFAR) in 2015 and 2018

Lopinavir / ritonavir and Abacavir and Lamivudine 40mg /10mg/60mg/30mg : Cipla – DND*i* in development

However, there are little clinical data on effectiveness and safety in routine care

Prospective study of **l**opinavir based ART for H**IV** **i**nfected childre**n** **g**lobally (LIVING study)

Aim: to evaluate the effectiveness of LPV/r pellets plus NRTI tablets (ABC or AZT and 3TC) **under field conditions in HIV-infected infants and young children in Africa**



LPV/r pellets

+

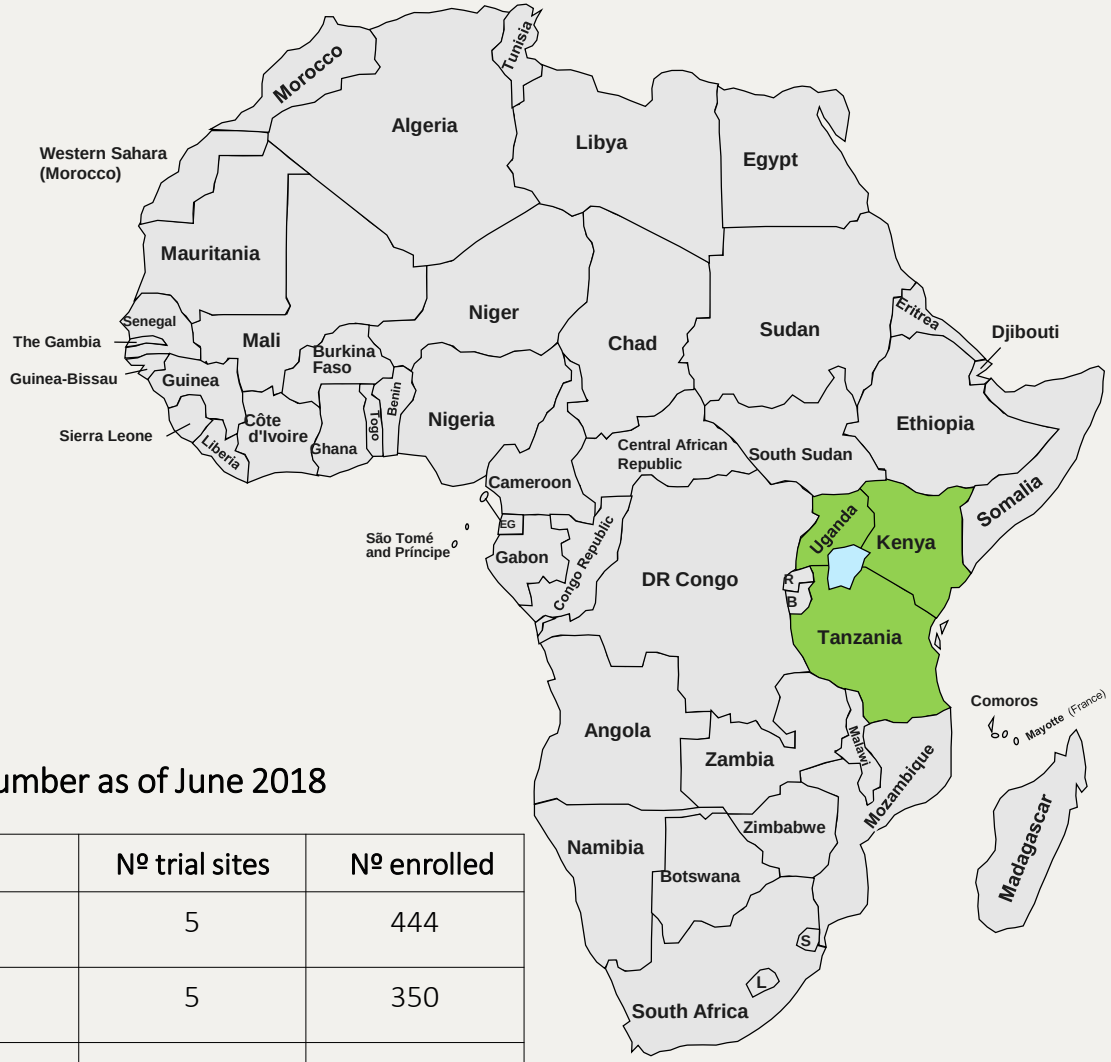
NRTI tablets

DNDi
Drugs for Neglected Diseases *initiative*

LIVING study design

- Single arm phase IIIb study, open-label, Prospective, non-randomized, non-comparative, multicenter, multi-country
- Inclusion : HIV-1 infected children:
  - Weight ≥3 and <25 kg at the time of enrolment. (Age is not an inclusion criterion)
  - ARV naïve, or already on first line liquid lopinavir based treatment, or Failing first line NNRTI based therapy.
  - Unable to swallow tablets

Current status of LIVING study



Enrolment number as of June 2018

Country	Nº trial sites	Nº enrolled
Kenya (n=350)	5	444
Uganda (n=350)	5	350
Tanzania (n=215)	2	207
Total		**1001**

DNDi
Drugs for Neglected Diseases *initiative*

LIVING study: inclusion and exclusion criteria

Inclusion

HIV-1 infected children:

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

Exclusion

- Planned or concurrent use of NNRTIs, integrase inhibitors, or PIs other than LPV/r.
- 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.

INTERIM RESULTS

PELLETS' FORMULATION OF LOPINAVIR/RITONAVIR IN CHILDREN: 48-WEEK EVOLUTION OF VIRAL SUPPRESSION ACROSS AGE CATEGORIES IN THE LIVING STUDY- Professor Dalton-IAS 2018-oral presentation

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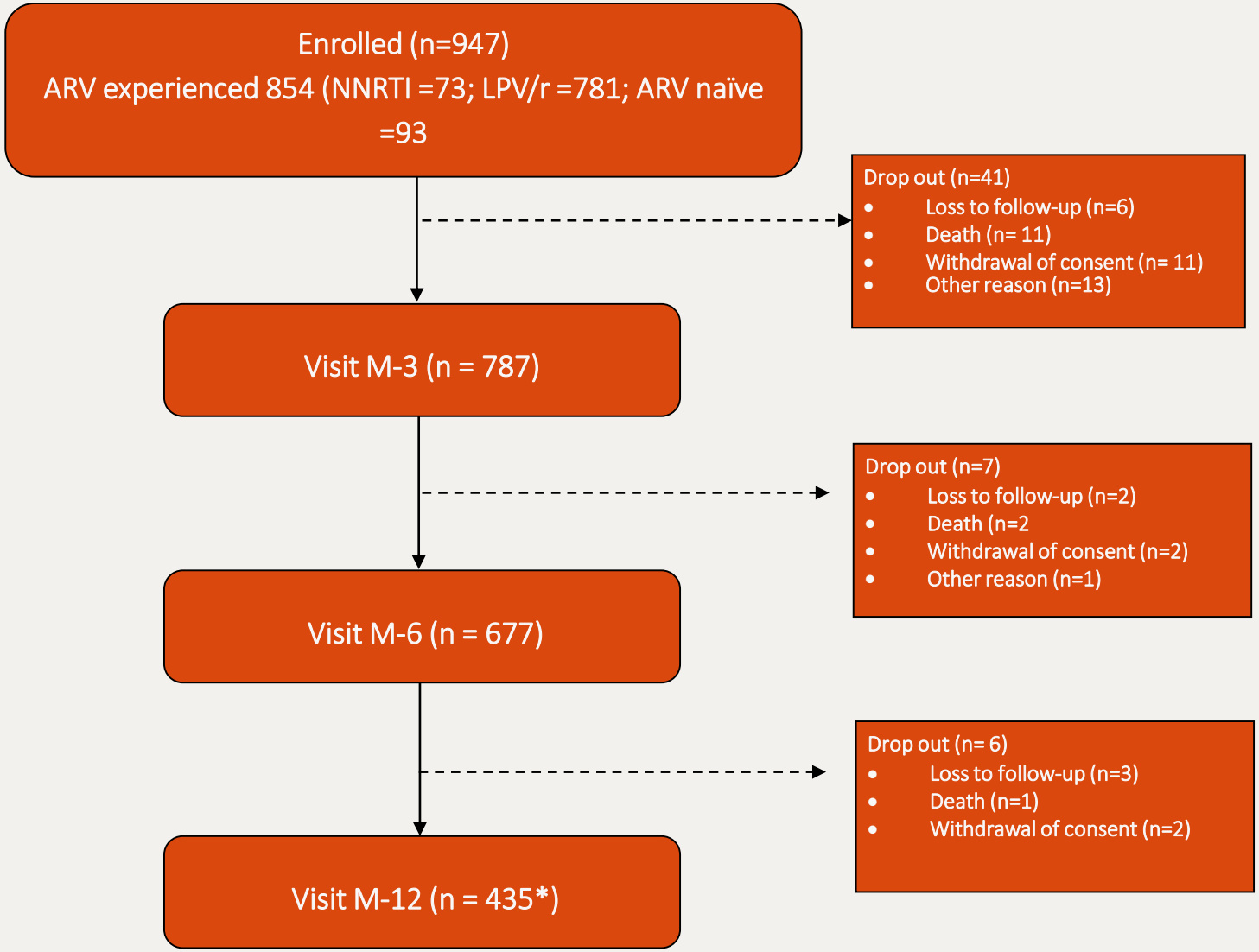
LIVING study status

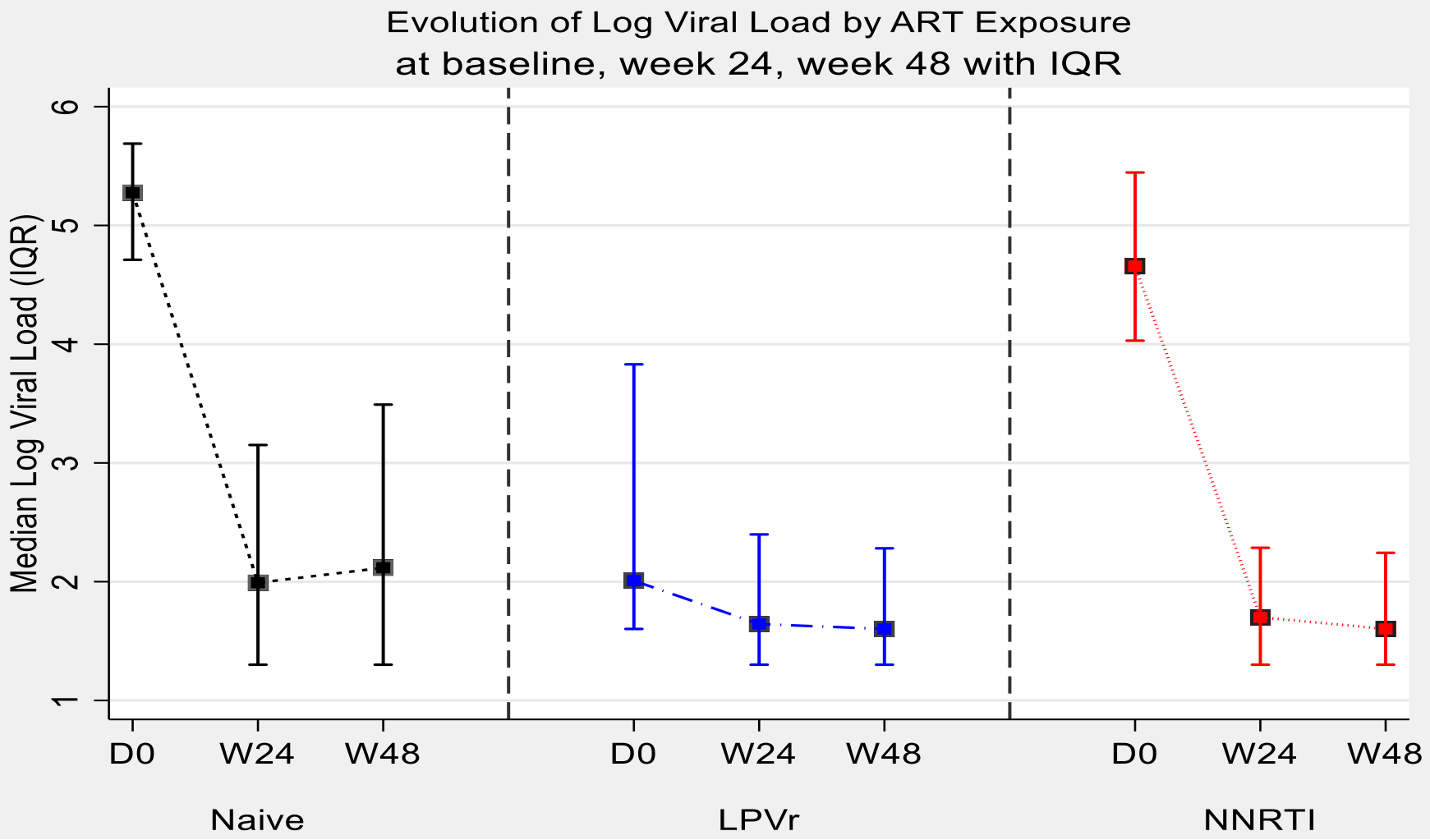


*Analysis focuses on 354 participants with complete set of CD4 and VL

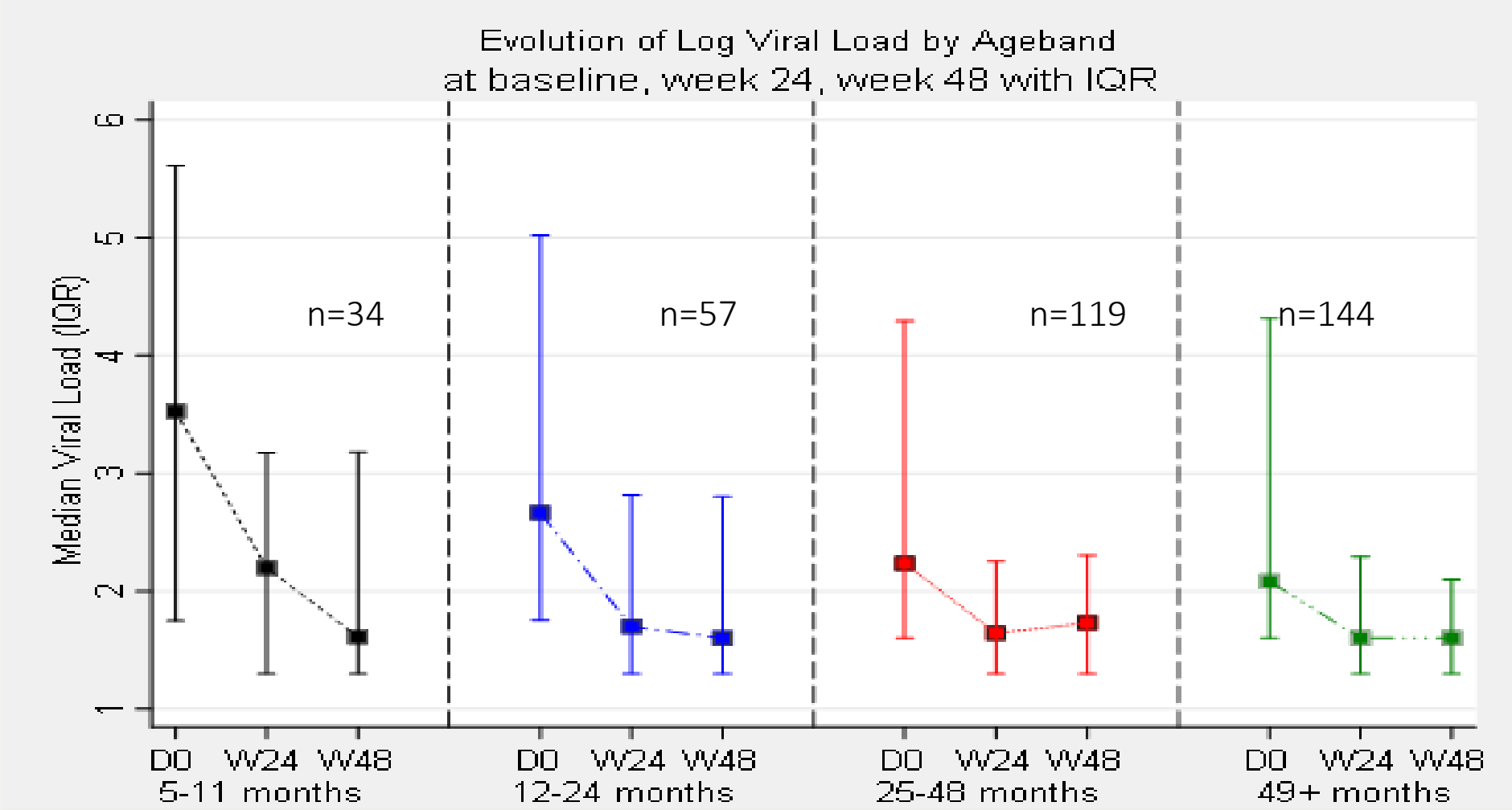
LIVING study: baseline characteristics (n= 354)

	ART-naïve (n=34)	Lopinavir (n=297)	NNRTI (n=25)	Total (354)
	Median(IQR)	median (IQR)	median (IQR)	median (IQR)
pre-enrolment ART duration (months)	0-0	25.3 (8.6- 45.5)	34.8 (11.5- 47.7)	26.2 (9.2- 45.7)
Age (months)	20.0 (11.0-36.0)	43.0 (25.0- 63.0)	55.0 (30.0- 65.0)	42.0 (24.0- 62.0)
Weight at baseline (kg)	9.2 (6.2-12.0)	13.7 (10.4- 16.0)	14.0 (12.0- 16.6)	13.2 (10.0- 16.0)
Viral load (log10 copies/ml)	5.4 (4.9-5.7)	2.0 (1.6- 3.8)	4.7 (4.0- 5.4)	2.4 (1.6- 4.6)

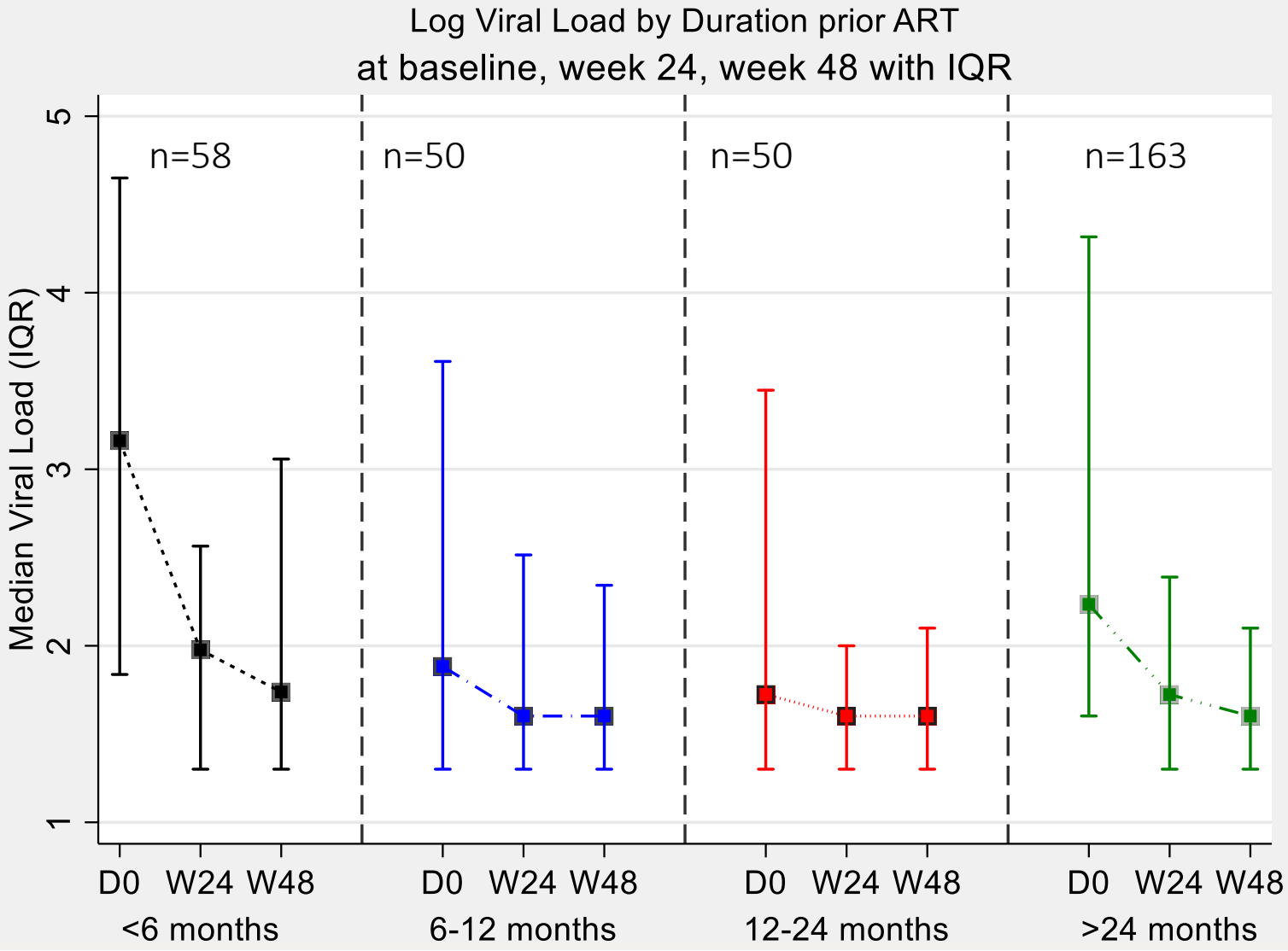
LIVING study: Viral load (log) suppression stratified by prior ART exposure



LIVING viral load (log) suppression stratified by age at enrolment

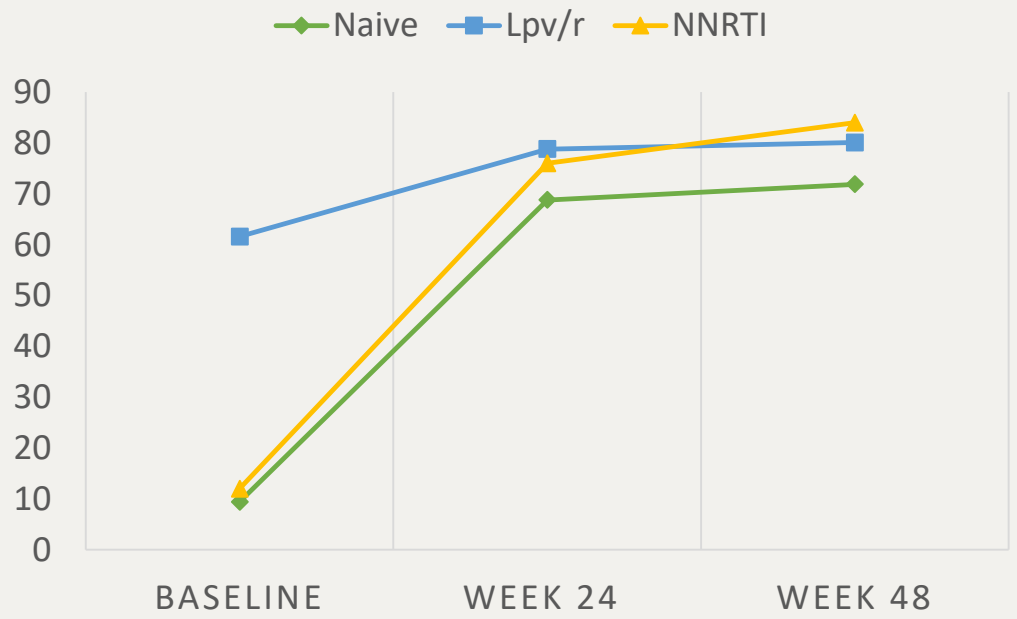


LIVING viral load (log) suppression stratified by duration of prior ART

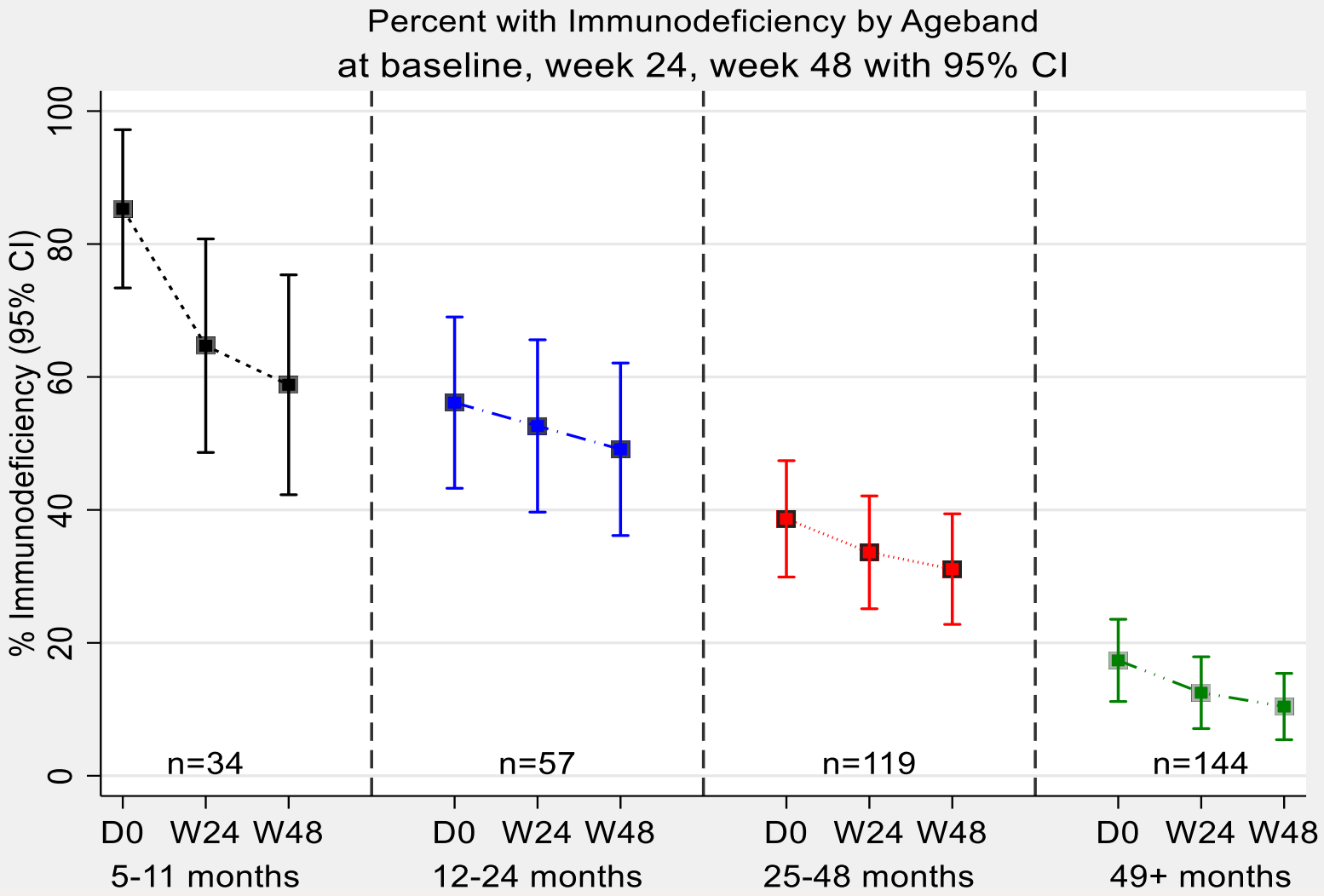


LIVING study: viral suppression stratified by prior ART exposure (% VL <400 copies/ml)

	BASELINE	WEEK 24	WEEK 48
Naive	9.4	68.8	71.9
LPV/r	61.6	78.8	80.1
NNRTI	12.0	76.0	84.0
Overall	**53.5**	**77.7**	**80.0**

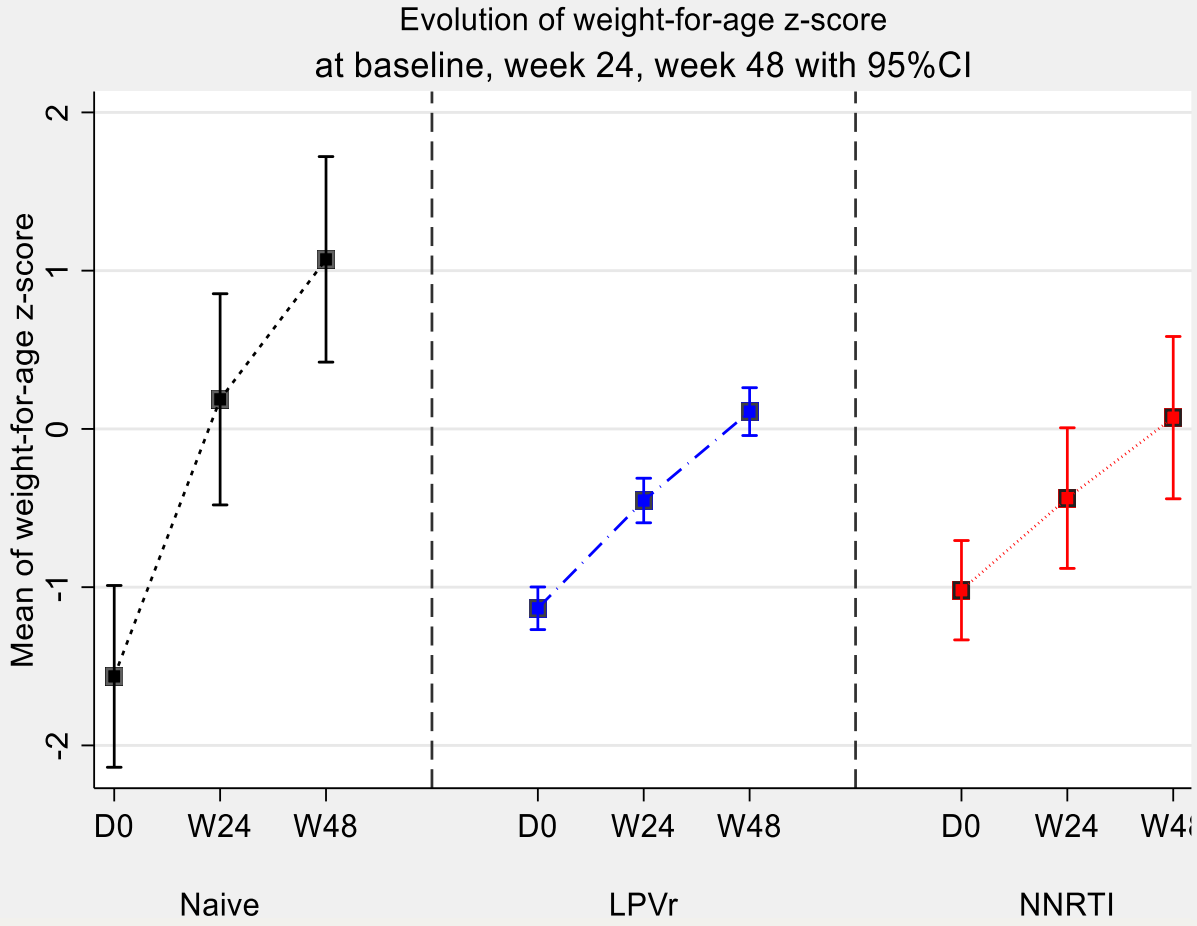


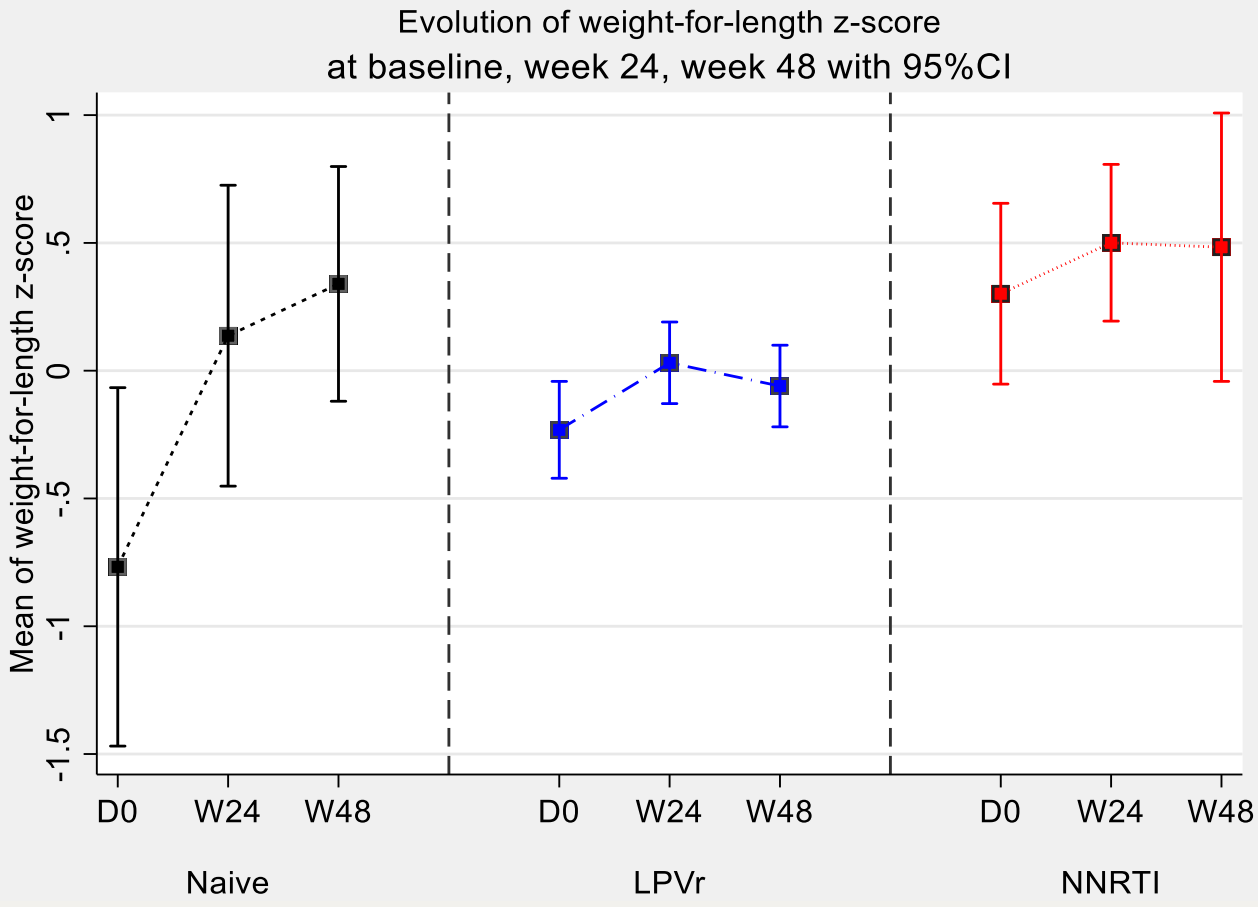
LIVING study: Reduction in immunodeficiency*



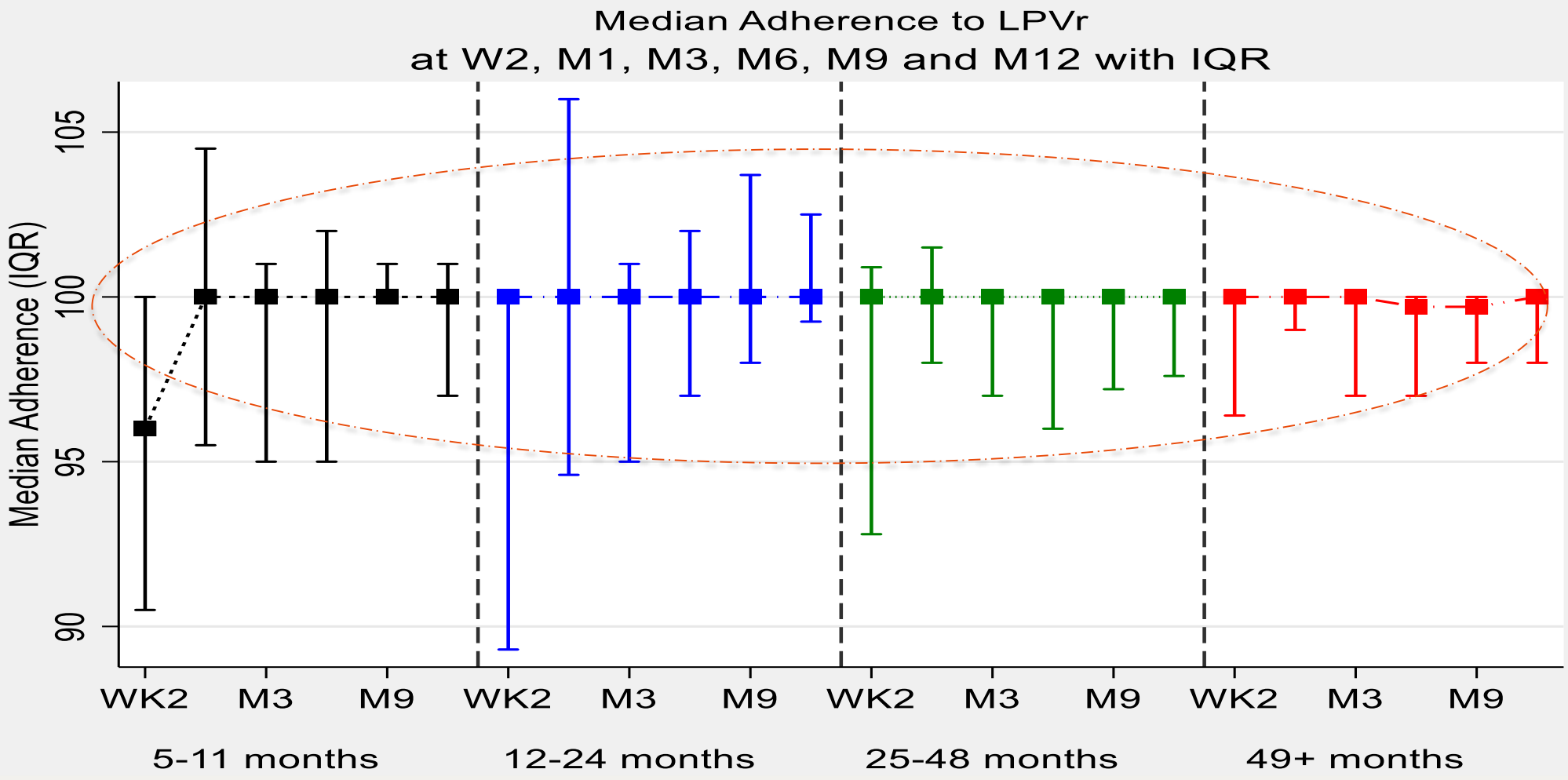
* Based on WHO classification of age-specific CD4% and count

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





LIVING study: Calculated adherence (pill counts)



LIVING Study: AEs and SAEs (top 10 most reported) n=947

- 915 AEs in 735 participants
- 34 SAEs in 25 participants

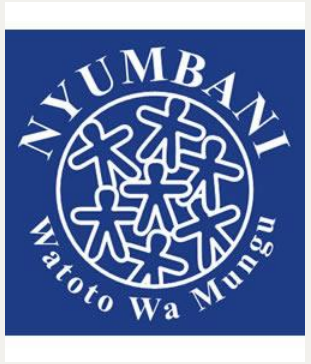
Adverse Event	FREQ
RESPIRATORY TRACT INFECTION	225
DIARRHOEA	41
GASTROENTERITIS	40
RHINITIS	38
COUGH	33
DERMATITIS	32
TINEA CAPITIS	31
NASOPHARYNGITIS	30
OTITIS MEDIA	23
MALARIA	22

Serious Adverse Event	FREQ
ACUTE GASTROENTERITIS	5
SEVERE MALARIA	4
PNEUMONIA	4
DIARRHOEA	3
SEVERE ACUTE MALNUTRITION	3
GASTROENTERITIS	1
NEUTROPENIA	1
HYPOALBUMINEMIA	1
SEPTICAEMIA	1
ELEVATED ALKALINE PHOSPHATASE	1

LIVING study : Conclusion from interim analysis

- 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.
- LPV/r pellets-based therapy was effective and well tolerated, with no unexpected safety concerns
- Data very supportive of LPV/r child-adapted formulations to improve compliance and clinical outcomes

Acknowledgements: Partners, investigators and study staff



Acknowledgements

UBS Optimus Foundation

& private individuals and foundations


Thank you for listening.
DNDi
Drugs for Neglected Diseases initiative