Could an Efavirenz-based therapy simplify a successful LPV/r-based therapy initiated before the age of two in HIV-infected children in West-Africa? The MONOD ANRS 12206 non inferiority trial

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Disclosures

- There are no financial conflicts of interest

Challenges with lifelong pediatric ART

- WHO recommends:
  - ART for all children <12 months (2008), <24 months (2010), <60 months (2013)
  - First-line lopinavir/ritonavir (LPV)-based ART

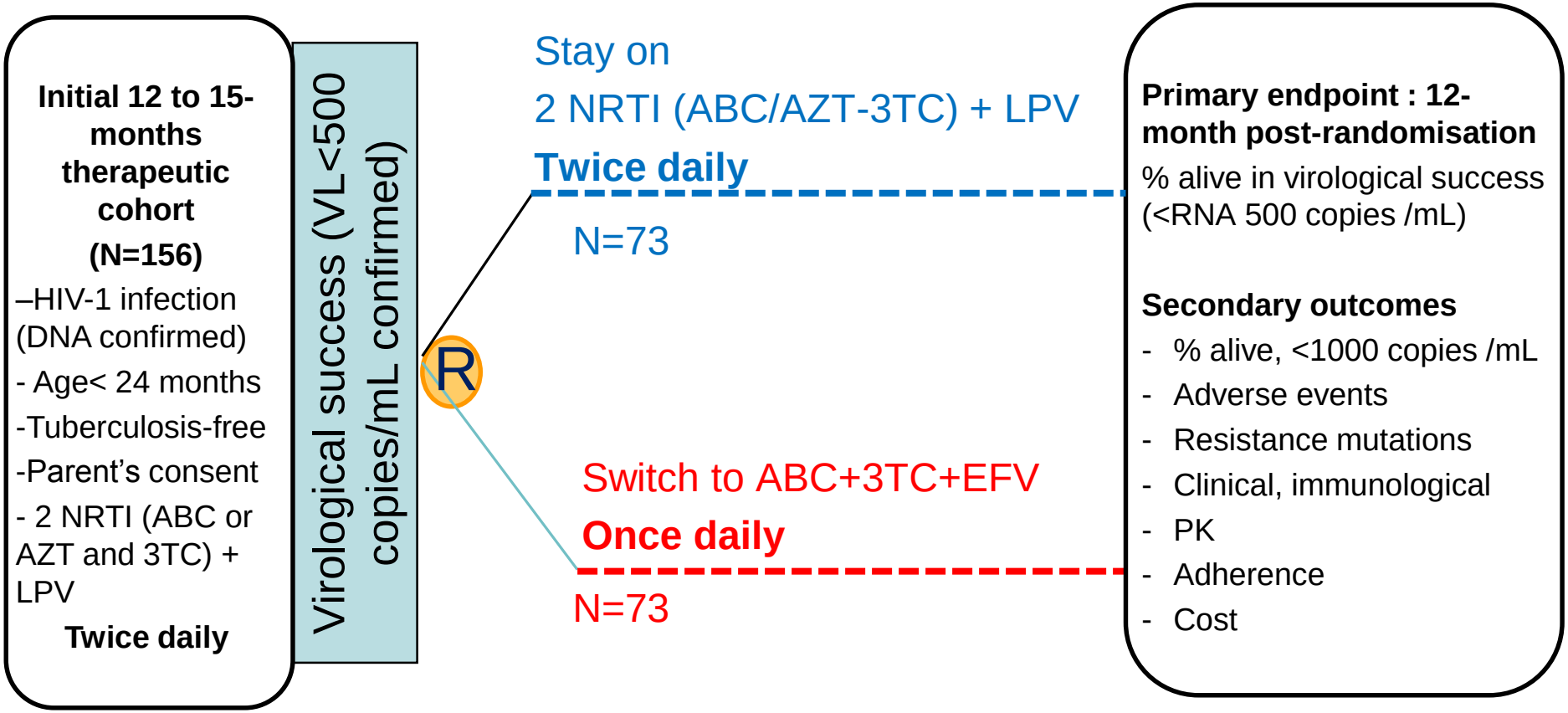
- Challenges of using protease inhibitors (PI)
  - Poor palatability
  - Potential metabolic complications
  - Cost and logistics
  - Interactions with tuberculosis treatment
  - Preserved as a second-line option

Question and hypothesis of the MONOD ANRS 12206 trial

- Would it be possible to simplify this early LPV-based regimen in children in virological success?
  - With a once-a-day ART: easier to use
  - Sparing PI in the context of poor access to second line regimen
    - NVP-based ART after LPV? NEVEREST 2 trial, JAMA 2010
    - EFV-based ART after LPV? NEVEREST 3 trial, CROI 2014

- HIV-infected children virologically suppressed after an initial 12-15 months of LPV could be simplified with a once-daily efavirenz-based therapy (EFV)

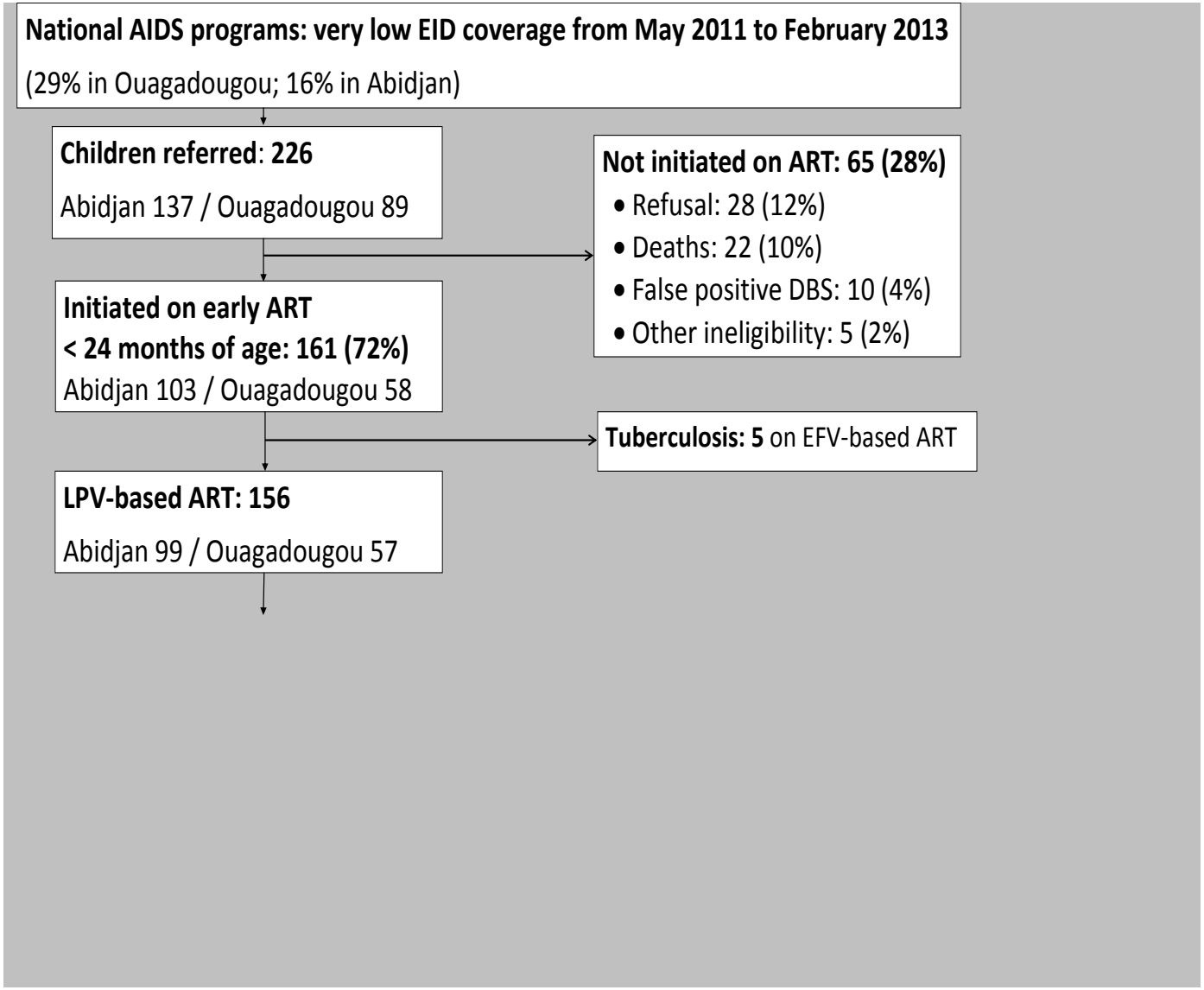
Trial design: non inferiority, open label phase 3 randomized clinical trial in Ouagadougou, Burkina Faso & Abidjan, Côte d'Ivoire



Non-inferiority: difference in % with RNA<500c/mL between arms: 14% (anticipated statistical power: 80%)

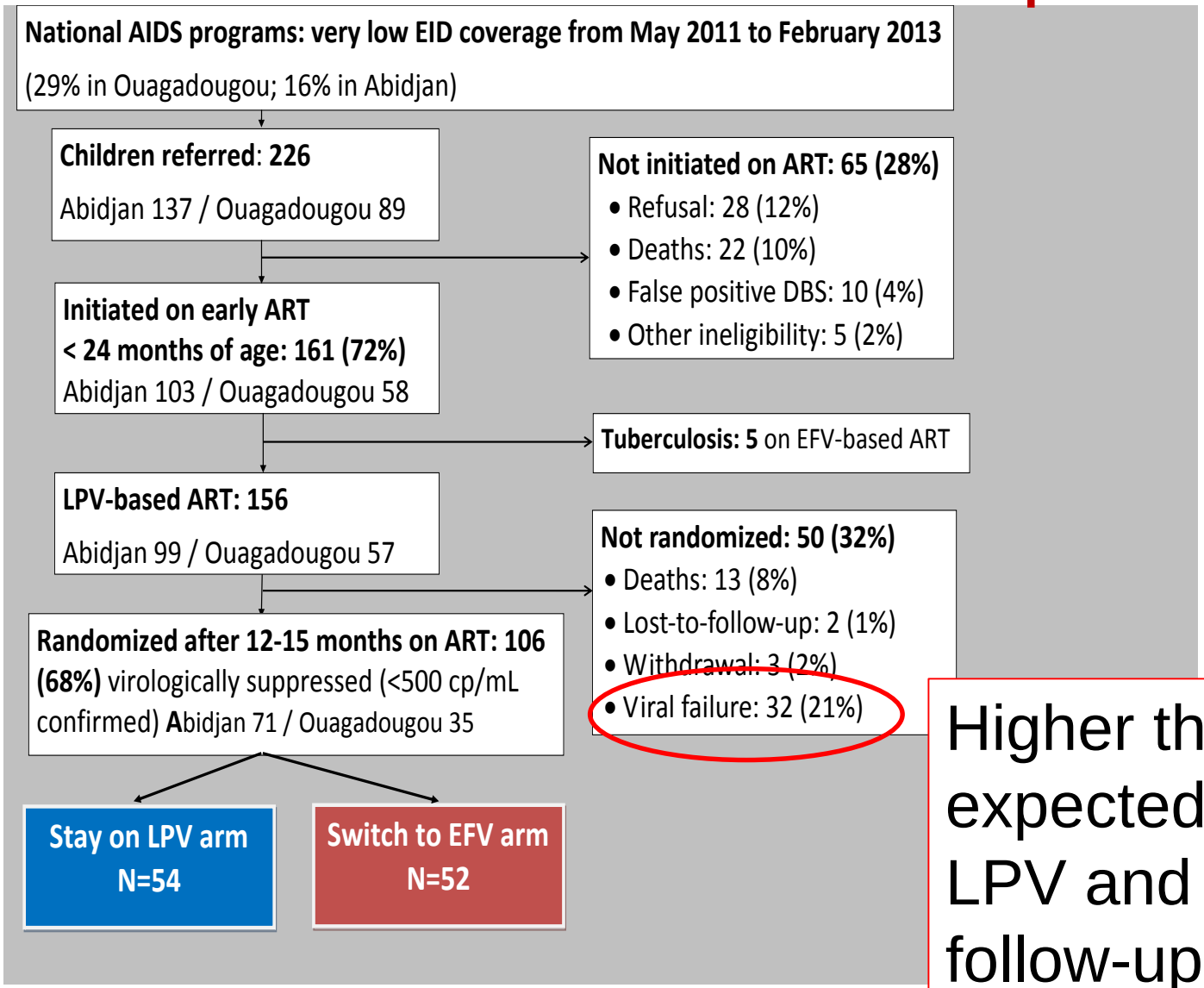
ClinicalTrial.gov registry number: NCT01127204

MONOD trial recruitment profile



See response to initial LPV ART: Posters P28, P34, P72

MONOD trial recruitment profile



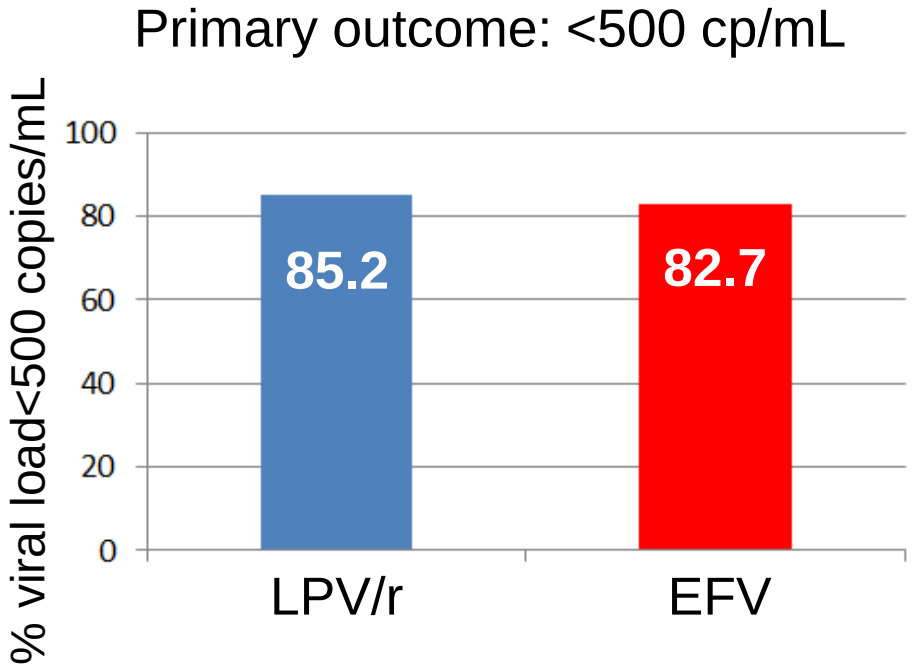
Higher than expected; still on LPV and under follow-up

See response to initial LPV ART: Posters P28, P34, P72

Characteristics of the 106 randomized children

Characteristics	N=106
Abidjan site, n (%)	71 (67)
Girl, n (%)	59 (56)
Maternal or child PMTCT intervention, n (%)	
Single-dose-NVP-based PMTCT	9 (8)
Other than single dose-NVP-based PMTCT	40 (38)
No PMTCT	**57 (54)**
At ART initiation, median age (months) (IQR)	13.7 (7.6-18.4)
Mean weight-for-age z-score (SD)	-2.3 (1.4)
WHO stage 3 or 4, n (%)	**58 (55)**
Median CD4% (IQR)	**21 (14-27)**
Mean viral load (log_{10} copies/mL), (SD)	6.3 (1.0)
At randomization, median age (months) (IQR)	26.6 (21.3-31.5)
Median CD4 % (IQR)	**35 (28-41)**

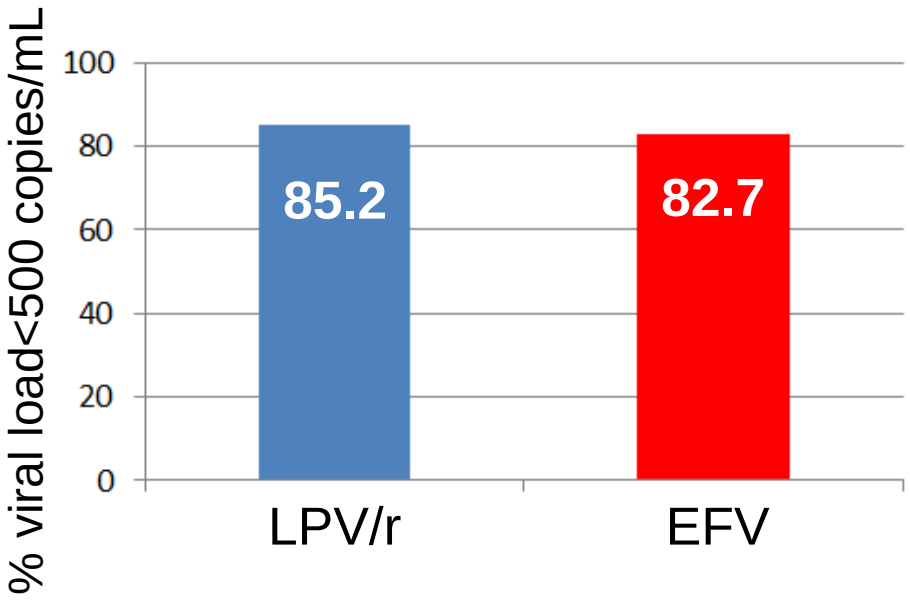
Primary outcome: virological success at M12 post-randomization per arm (N=106)



Rate of success (<500 cp/mL) in the LPV/r arm minus rate in EFV arm
Difference = -2.5% (95% CI: -16.5; 11.5)

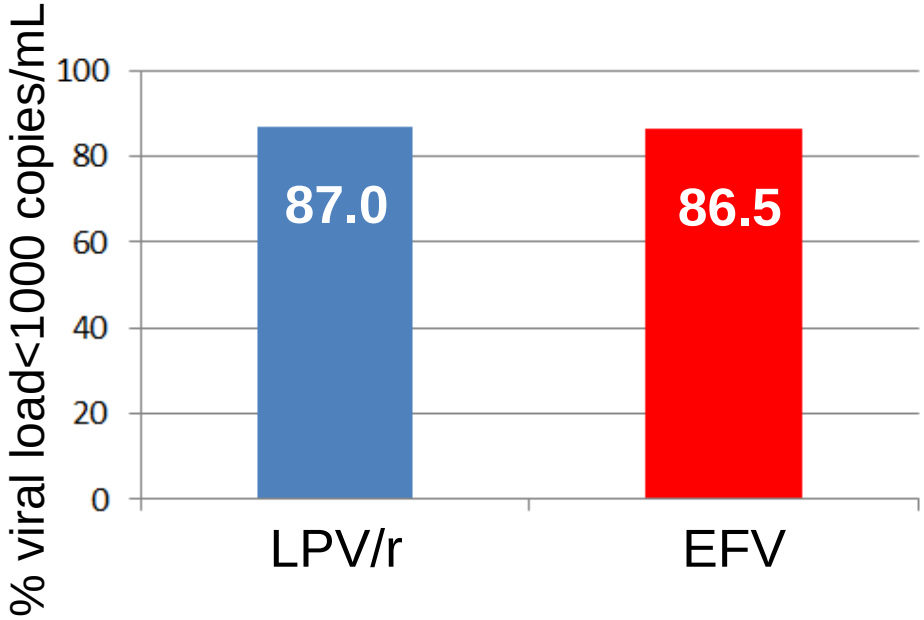
Primary outcome: virological success at M12 post-randomization per arm (N=106)

Primary outcome: <500 cp/mL



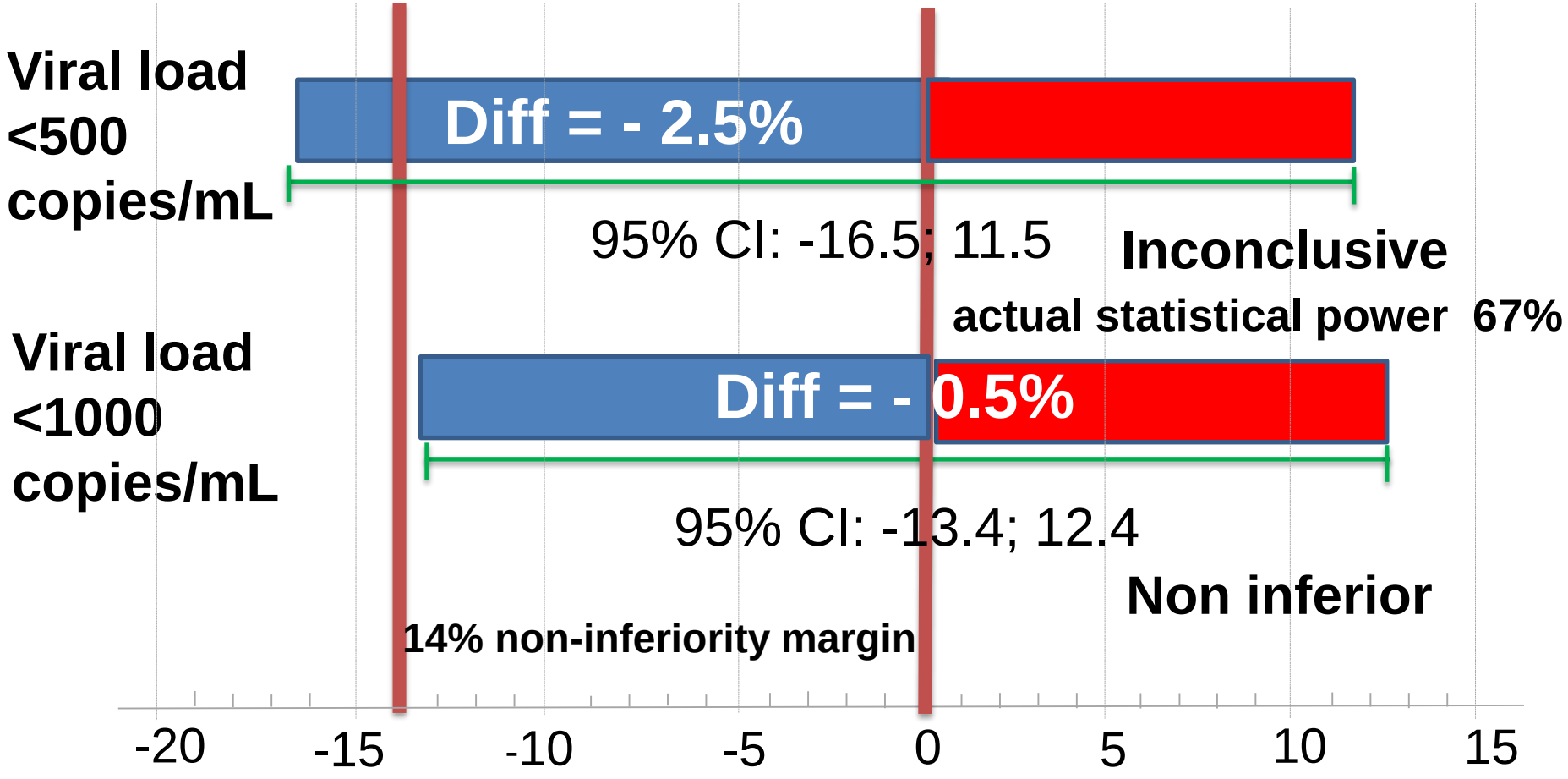
Rate of success (<500 cp/mL) in the LPV/r arm minus rate in EFV arm
Difference = -2.5% (95% CI: -16.5; 11.5)

Secondary outcome: <1,000 cp/mL



Rate of success (<1000 cp/mL) in the LPV/r arm minus rate in EFV arm
Difference = -0.5% (95% CI: -13.4; 12.4)

Viral success rate in LPV/r arm minus rate in EFV arm Difference of risk and 95% CI



Serious Adverse Events (SAE) per arm

Outcomes	LPV/r N=54	EFV N=52	P-value
Hospitalizations and clinical SAE	**3***	**3****	0.10
Sleeping disorders after switch	**2 (3.7)**	**3 (5.8)**	0.67
Grade 3 and 4 biological adverse events			
Anemia	1 (1.9)	2 (3.8)	0.61
Neutropenia	**10 (18.5)**	**1 (1.9)**	**<0.01**
Thrombopenia	1 (1.9)	0 (0.0)	1.00
Hypertransaminasemia AST or ALT	1 (1.9)	2 (3.8)	1.00
Hyperbilirubinemia	3 (5.6)	2 (3.8)	1.00
Hyperamylasemia	0 (0.0)	2 (3.8)	0.24

*1 malaria, 2 gastroenteritis ** 1 gastroenteritis , 1 pneumonia, 1 upper tract infection with malaria.
No other biological SAE including glycemia, cholesterolemia, triglyceridemia, creatininemia, lipasemia.

Resistance mutation profiles

13/14 children (VL> 1, 000 cp/mL) had a genotype before ART initiation and at 12-month

	LPV arm (n=7)	EFV arm (n=7)
Genotype performed	7	6
At least one drug resistance mutation (DRM)	5	5
NNRTI mutations: EFV/NVP K103N, Y181C, P225H	4 All transmitted (PMTCT) 0 acquired	5 2 transmitted (PMTCT) 3 acquired
NRTI mutations: 3TC M184V	2	4
PI mutations	0	0

Conclusion

- Access to EID and ART before age two still remains challenging in West Africa
- Children alive, in care, with VL<500 cp/mL after 12-15 months of LPV-ART were fewer than expected (68%)
- We could not demonstrate non-inferiority for the switch strategy based on the primary outcome (VL<500 cp/mL)
- We did demonstrate non-inferiority based on the secondary outcome (VL <1,000 cp/mL)
- Switch to a simplified EFV-based therapy is safe
- High frequency of transmitted NNRTI-DRM after PMTCT.
- Switch to EFV-based regimen could be a valuable individual strategy in virologically suppressed children with good clinical and adherence profiles, and not exposed to any PMTCT intervention

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Coordination center	Promotor
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