

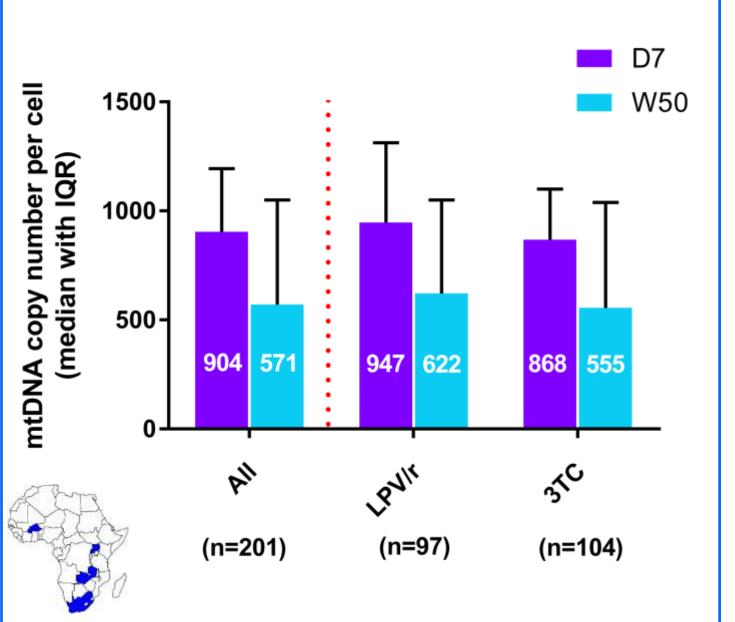
Lopinavir/ritonavir Induces Mitochondrial Toxicity in HIV-exposed Uninfected Children

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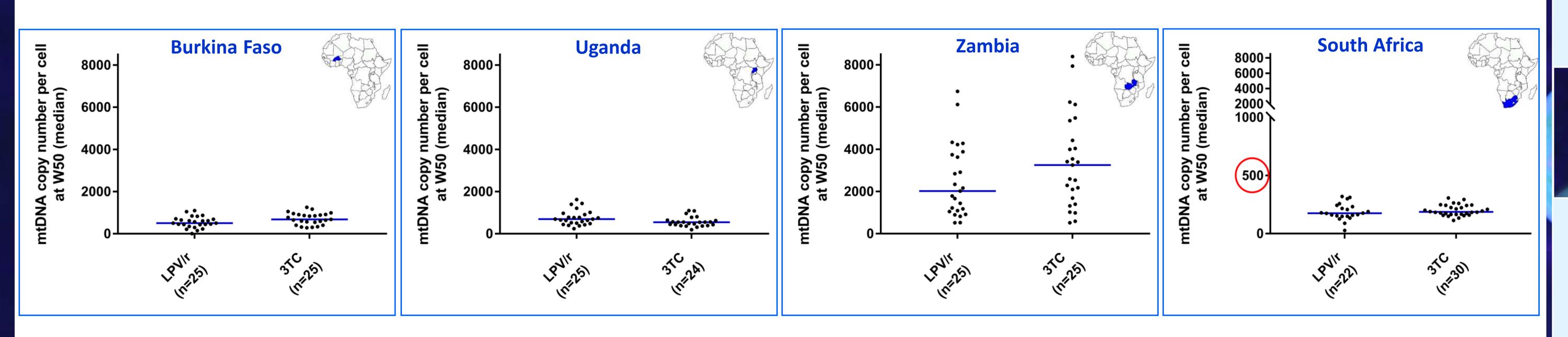
mtDNA depletion

Mitochondrial DNA copy number at day 7 and after one year of PrEP



• Overall, the mtDNA copy number per cell markedly decreased after one year of prophylactic treatment and irrespective of the drug used.

> **14.9% of children** (19.6% in the LPV/r arm and 10.6% in the • 3TC arm) presented a **mtDNA depletion**, the vast majority of them were in South Africa. There was significantly more children with a mtDNA depletion for the LPV/r treatment in this site compared to the 3TC one.



• Children from Burkina Faso and Uganda presented similar levels of mtDNA copy number per cell at W50. Children from Zambia showed the highest whereas those from South Africa showed the lowest.

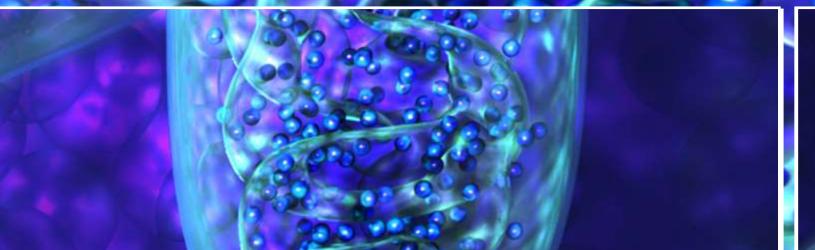
Risk factors associated with a mtDNA depletion after one year of PrEP

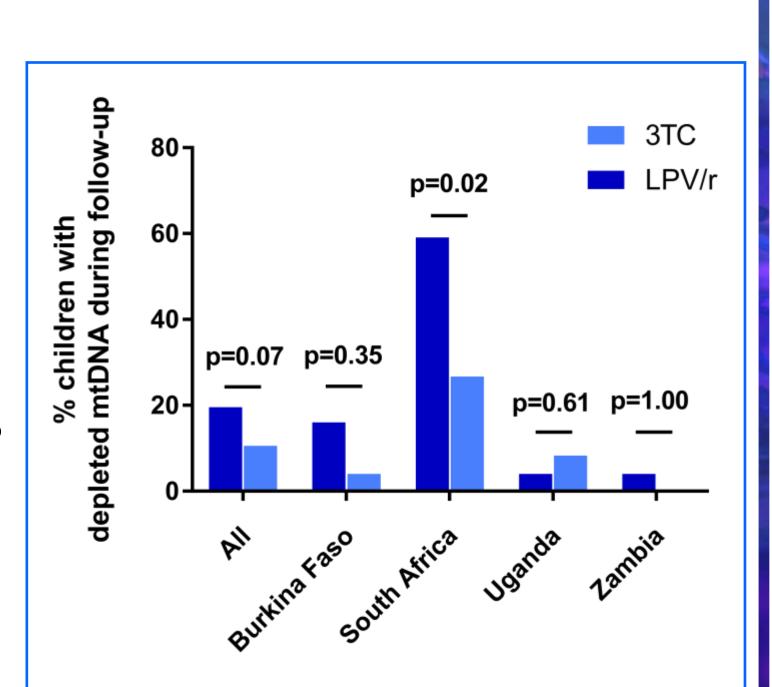
Independent variable	OR	95% CI	p value	AOR	95% CI	p value
Gender						
Boy versus Girl	1.44	0.66-3.19	0.36			
Site						
Burkina Faso versus Zambia	5.44	0.61-48.40		6.33	0.70-57.61	
South Africa versus Zambia	33.19	4.25-259.3	< 0.01	49.94	6.05-412.5	< 0.01
Uganda versus Zambia	3.20	0.32-31.83		4.22	0.41-43.55	
PrEP						
LPV/r versus 3TC	2.06	0.95-4.59	0.08	3.13	1.22-8.04	0.02
Duration of pre-partum maternal ARV treatment (weeks)	1.09	1.01-1.17	0.02			
Duration of breastfeeding (weeks)	0.97	0.94-1.01	0.11			
Mother plasma HIV RNA (copies/mL)						
Uncontrolled (≥1000) versus Controlled (<1000) at D7	1.70	0.78-3.71	0.18	2.22	0.89-5.49	0.09
Uncontrolled (≥1000) versus Controlled (<1000) at W38	1.11	0.48-2.57	0.81			
Gestationnal age (weeks)	0.88	0.70-1.10	0.26			
Weight of the baby at D7 (kg)	0.58	0.24-1.43	0.24			
Haemoglobin concentration at D7 (g/dL)	1.00	0.93-1.07	0.98			

OR, odd ratio; AOR, adjusted odd ratio; CI, confidence interval

the 25th Conference on Retroviruses and Opportunistic Infections, March 4-7, 2018, Boston, United States of America







value

0.01

After adjustment, LPV/r treatment was associated with a mtDNA depletion after one year of PrEP.

ntroduction

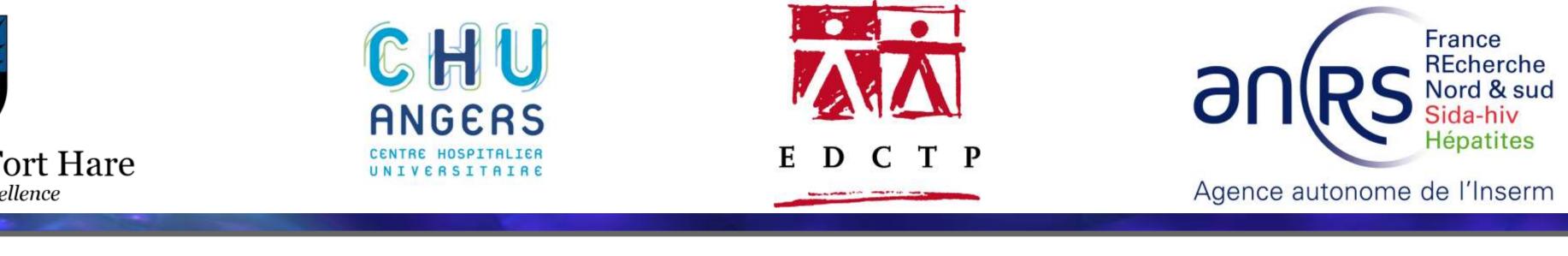
- Adverse outcomes in HIV-exposed uninfected (HEU) children have been reported, including **mitochondrial toxicity** (1).
- HEU children are exposed to HIV and ARV during the pregnancy and breastfeeding periods.
- Pre-exposure prophylaxis (**PrEP**) is widely deployed in populations at risk Mitochondria of acquiring HIV but still not widely promoted among HEU children.
- Beside the well-known side effect of NRTI on mitochondria (2), protease inhibitors such as LPV/r were not reported to be mitotoxic.
- The aim of this study was to quantify the mitochondrial toxicity of lopinavir/ritonavir (LPV/r) and lamivudine (3TC) used as PrEP among breastfed HEU children.

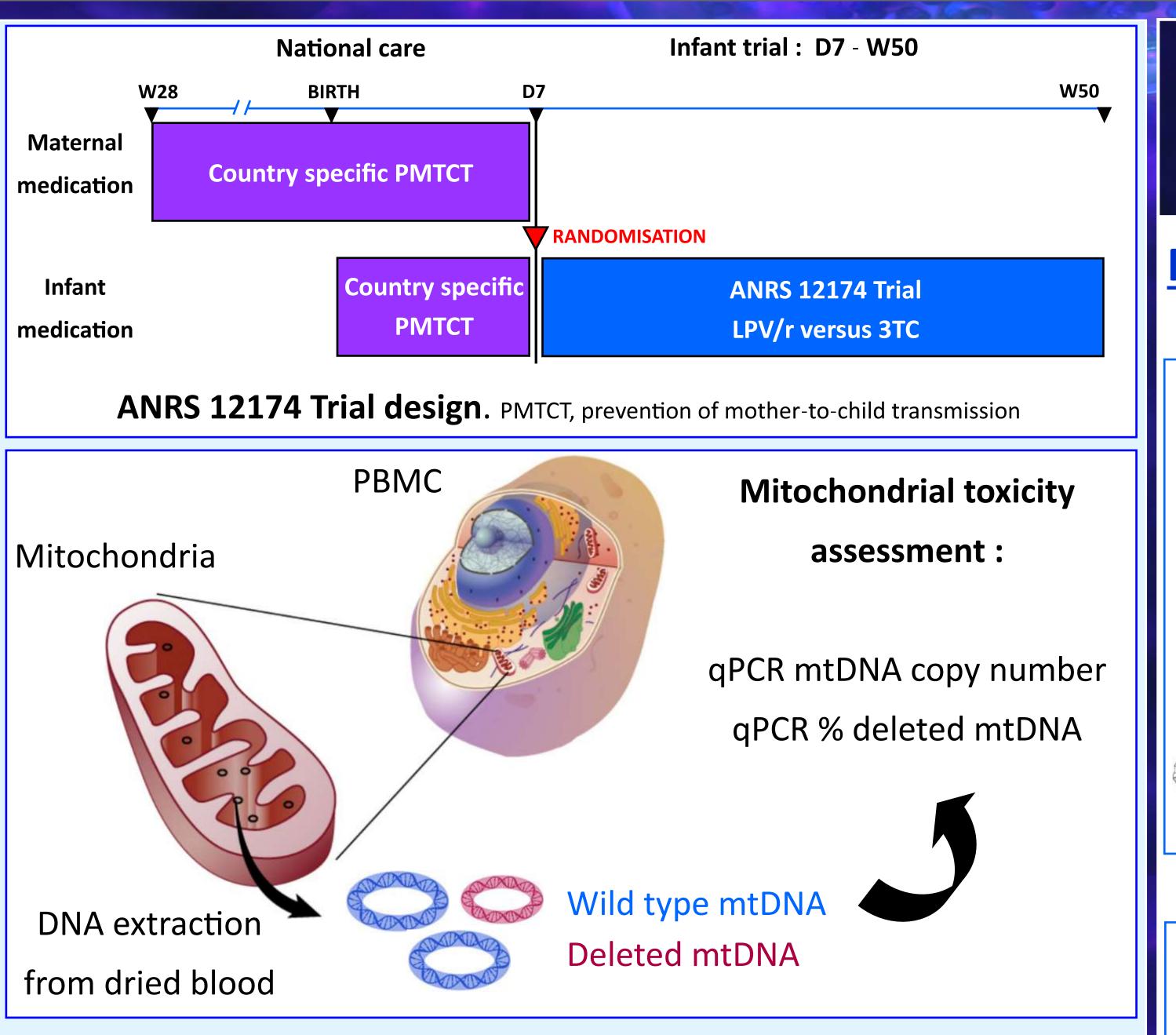
Method

- <u>mtDNA depletion</u> at W50 was defined by a mtDNA copy number per cell • 201 children from the ANRS 12174 trial were randomly included in this (mtDNA) 30% lower than its value at D7. study with a sex and treatment ratio around 1.
- The ANRS 12174 trial was conducted in four african countries (Burkina Faso, South Africa, Uganda and Zambia) between 2009 and 2014. 1273 • Wilcoxon rank test was used to compare continous variables. Multivariate logistic regression were performed to identify the risk **breastfed HEU children** born to HIV-infected mothers were recruited (3). factors associated with a mtDNA depletion and an increase proportion of • At day seven (D7), children were randomized to receive either **3TC** or deleted mtDNA at W50.
- **LPV/r** as PrEP until the end of breastfeeding (max 50 weeks W50).

Conclusions

- A marked decrease of mtDNA copy number per cell was mtDNA content and/or level of deleted mtDNA consistent with observed in children under PrEP, significantly and mitochondrial disorders. independently more important for those taking LPV/r • Because mitochondrial toxicity in HEU children was reported to be persistent until 3 years and reversible in some regimen.
- Unexpectedly, the proportion of deleted mtDNA, assessed circumstances. long-term assessment these ot for the first time in this population, was high at birth and mitochondrial parameters among these children is remained unchanged at the end of the prophylaxis period. needed.
- Mitochondrial toxicity of LPV/r came as a surprise since LPV/r was not reported as responsible for this adverse event in the literature.
- At an individual level, whether none of the children included in this study presented any clinical symptom of mitochondrial diseases, several of them showed level of





- We used definitions of mitochondrial DNA parameters according to a reference center for mitochondrial disorders :
- <u>% deleted mtDNA</u> at W50 was considered at risk when it exceeds 40%.

<u>References</u>

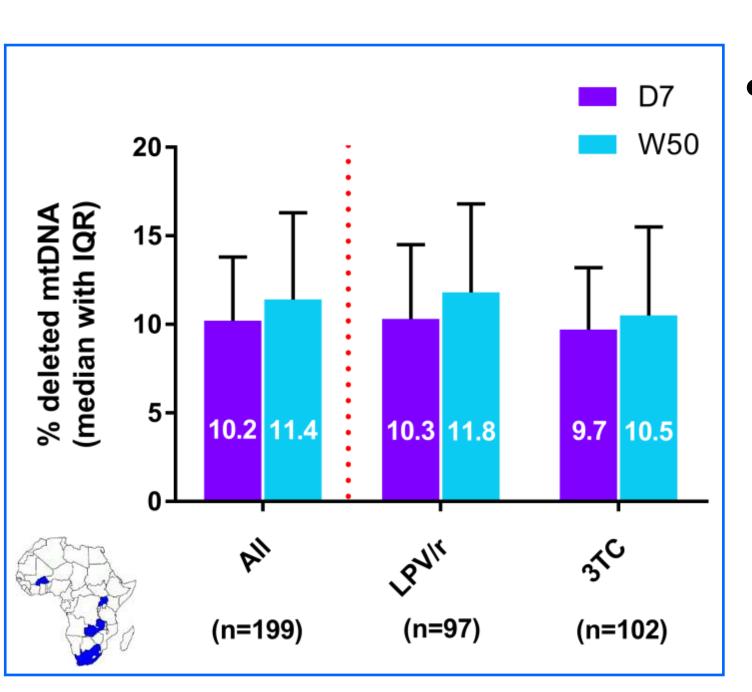
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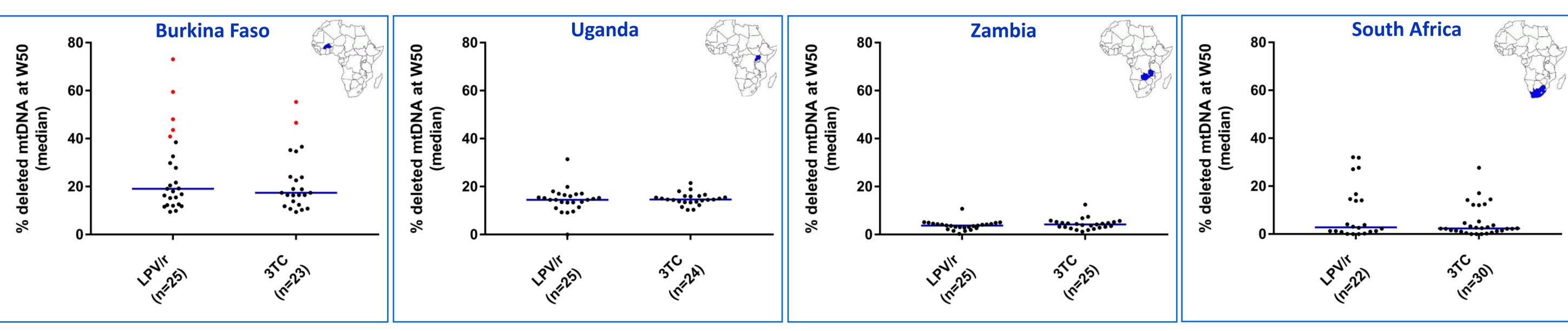
[2]Kohler J, et al. A Brief overview of mechanisms of mitochondrial toxicity From NRTIs. *Mitochondrial DNA A* DNA Mapp Seq Anal, 2016, 27(3):1685-7

[3]Nagot N, et al. Lopinavir/ritonavir versus Lamivudine peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: the PROMISE-PEP trial Protocol ANRS 12174. BMC Infe Dis, 2012, 12:246.

This work was funded by the Pierre Bergé endowment fund in collaboration with Sidaction and sponsored by the French National Agency for Research on AIDS and Viral Hepatitis [ANRS#12174]

Proportion of deleted mtDNA at day 7 and after one year of PrEP





Risk factors associated with an increase deleted mtDNA rate after one year of PrEP

Independent variable	OR	95% CI	p value	AOR	95% CI	p value
Gender						
Boy versus Girl	0.98	0.56-1.70	0.93			
Site						
Burkina Faso versus South Africa	3.75	1.64-8.59		2.99	1.27-7.04	
Uganda versus South Africa	3.88	1.70-8.85	< 0.01	4.04	1.73-9.45	< 0.01
Zambia versus South Africa	1.75	0.79-3.92		1.69	0.74-3.85	
PrEP						
LPV/r versus 3TC	1.60	0.91-2.80	0.10	1.42	0.79-2.57	0.25
Duration of pre-partum maternal ARV treatment (weeks)	0.99	0.93-1.04	0.61			
Duration of breastfeeding (weeks)	1.00	0.98-1.03	0.89			
Mother plasma HIV RNA (copies/mL)						
Uncontrolled (≥1000) versus Controlled (<1000) at D7	0.91	0.52-1.59	0.76			
Uncontrolled (≥1000) versus Controlled (<1000) at W38	0.64	0.35-1.16	0.14	0.42	0.20-0.88	0.02
Gestationnal age (weeks)	1.05	0.89-1.24	0.58			
Weight of the baby at D7 (kg)	0.39	0.20-0.78	0.01	0.37	0.18-0.75	0.01
Haemoglobin concentration (g/dL)	0.99	0.95-1.04	0.70			

OR, odd ratio; AOR, adjusted odd ratio; Cl, confidence interva



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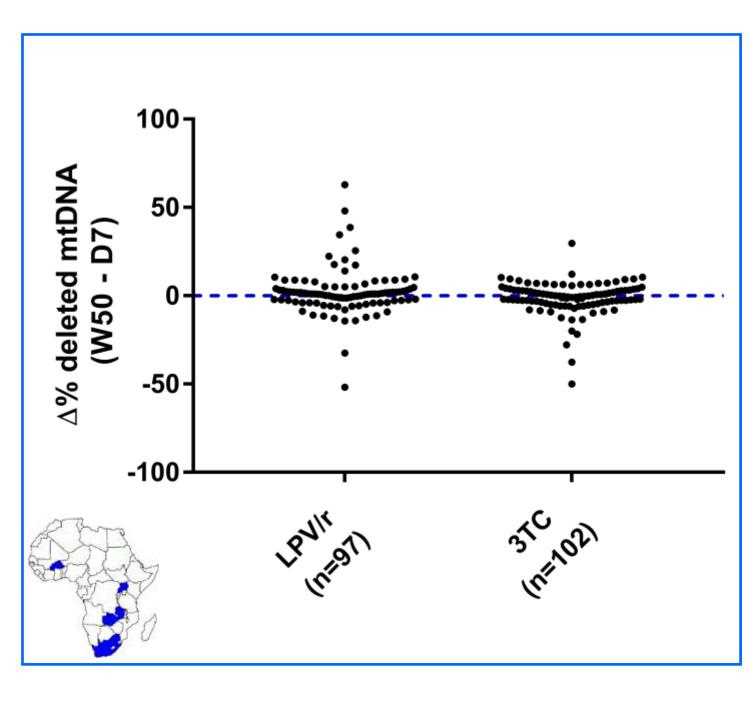


Poster #878

Proportion of deleted mtDNA

D7 • Overall, the proportion of deleted mtDNA remained unchanged after one year of prophylactic treatment, despite being high at day 7.

> During the follow-up, 51.8% of children presented an increase • in the proportion of deleted mtDNA (55.3% in the LPV/r arm and 44.7% in the 3TC arm).



• Children from Burkina Faso and Uganda presented the highest rates of deleted mtDNA, children from Zambia and South Africa the lowest. Seven children (5 in the LPV/r arm and 2 in the 3TC arm), all in Burkina Faso, presented a deletion rate over 40% (red dots•).

> After adjustment, LPV/r treatment was not associated with an increase proportion of deleted mtDNA after one year of PrEP.