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

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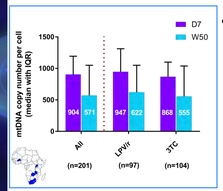
Poster #878

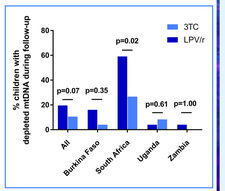
mtDNA depleon

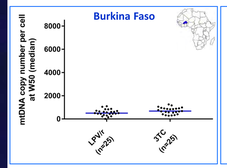
Mitochondrial DNA copy number at day 7 and a er one year of PrEP

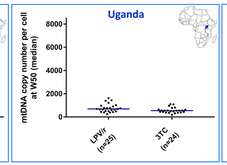


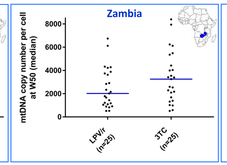
- Overall, the mtDNA copy number per cell markedly decreased a er one year of prophylacc treatment and irrespecv e of the drug used.

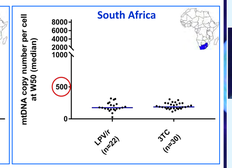
14.9% of children (19.6% in the LPV/r arm and 10.6% in the 3TC arm) presented a **mtDNA deple on**, the vast majority of them were in South Africa. There was signic antly more children with a mtDNA depleon for the LPV/r treatment in this site compared to the 3TC one.











- 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 deple.on a er one year of PrEP

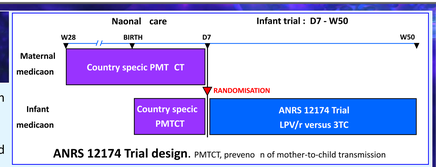
Independent variable	OR	95% CI	p value	AOR	95% CI	p value
Gender						
Boy versus Girl	1.44	0.66-3.19	0.36			
Site						
Burkina Faso versus Zambia	5.44	0.61-48.40		6.33	0.70-57.61	
South Africa versus Zambia	33.19	4.25-259.3	<0.01	49.94	6.05-412.5	<0.01
Uganda versus Zambia	3.20	0.32-31.83		4.22	0.41-43.55	
PrEP						
LPV/r versus 3TC	2.06	0.95-4.59	0.08	**3.13**	**1.22-8.04**	**0.02**
Durao n of *pre-partum* maternal ARV treatment (weeks)	1.09	1.01-1.17	0.02			
Durao n of breas eeding (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			
Gestaonnal ag e (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 concentraon a t D7 (g/dL)	1.00	0.93-1.07	0.98			

OR, odd ra.o; A OR, adjusted odd rao; CI, condence interval

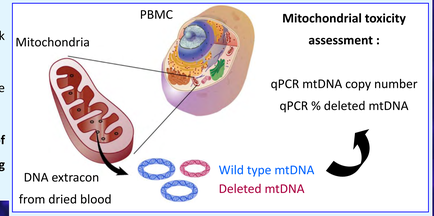
A er adjustment, **LPV/r treatment was associated with a mtDNA depleon a er one year of PrEP.**

Introducon

- 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 breas eeding periods.
- Pre-exposure prophylaxis (**PrEP**) is widely deployed in populaons at risk of acquiring HIV but sll not widely promoted among HEU children.
- Beside the well-known side e ect of NRTI on mitochondria (2), protease inhibitors such as LPV/r were not reported to be mitotoxic.
- **The aim of this study was to quanf y the mitochondrial toxicity of lopinavir/ritonavir (LPV/r) and lamivudine (3TC) used as PrEP among breas ed HEU children.**



ANRS 12174 Trial design. PMTCT, preveno n of mother-to-child transmission



Method

- 201 children from the ANRS 12174 trial were randomly included in this study with a sex and treatment rao ar ound 1.
- The ANRS 12174 trial was conducted in four african countries (Burkina Faso, South Africa, Uganda and Zambia) between 2009 and 2014. 1273 **breas ed HEU children** born to HIV-infected mothers were recruited (3).
- At day seven (D7), children were randomized to receive either **3TC** or **LPV/r** as PrEP un l the end of breas eeding (max 50 weeks W50).
- We used deni ons of mitochondrial DNA parameters according to a reference center for mitochondrial disorders :

- **mtDNA depleon** at W50 was dened by a mtDNA copy number per cell (mtDNA) 30% lower than its value at D7.

- **% deleted mtDNA** at W50 was considered at risk when it exceeds 40%.

- Wilcoxon rank test was used to compare connous variables. Mulv ariate logisc regression were performed to idenf y the risk factors associated with a mtDNA depleon and an increase proporon of deleted mtDNA at W50.

Conclusions

- **A marked decrease of mtDNA copy number per cell was observed in children under PrEP, significantly and independently more important for those taking LPV/r regimen.**
- **Unexpectedly, the proportion of deleted mtDNA, assessed for the first time in this population, was high at birth and remained unchanged at the end of the prophylaxis period.**
- **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 mtDNA content and/or level of deleted mtDNA consistent with mitochondrial disorders.
- Because mitochondrial toxicity in HEU children was reported to be persistent until 3 years and reversible in some circumstances, **long-term assessment of these mitochondrial parameters among these children is needed**.

References

[1]Aldrovandi G, et al. Anr etroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected mothers. *Pediatrics*, 2009, 124(6):e1189-97.

[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 breas eeding: the PROMISE-PEP trial Protocol ANRS 12174. *BMC Infe Dis, 2012, 12:246.*

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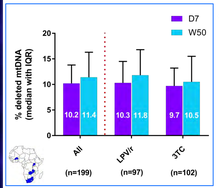
Proporon o f deleted mtDNA

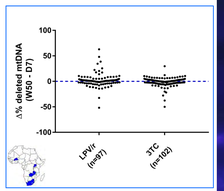
Proporon of dele ted mtDNA at day 7 and a er one year of PrEP

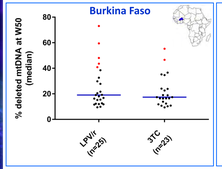


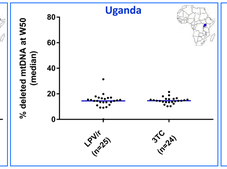
- Overall, the proporon of deleted mtDNA remained unchanged a er one year of prophylacc treatment, despite being high at day 7.

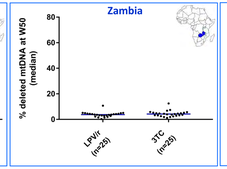
During the follow-up, 51.8% of children presented an increase in the proporon of deleted mtDNA (55.3% in the LPV/r arm and 44.7% in the 3TC arm).

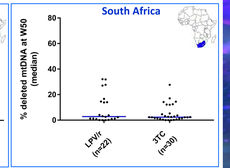
- Children from Burkina Faso and Uganda presented the highest rates of deleted mtDNA, children from Zambia and South Africa the lowest. Seven children (5 in the LPV/r arm and 2 in the 3TC arm), all in Burkina Faso, presented a deleon r ate over 40% (red dots•).











Risk factors associated with an increase deleted mtDNA rate a er 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**
Durao n of *pre-partum* maternal ARV treatment (weeks)	0.99	0.93-1.04	0.61			
Durao n of breas eeding (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
Gestaonnal ag e (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 concentraon (g/dL)	0.99	0.95-1.04	0.70			

OR, odd rao; A OR, adjusted odd rao; CI, condence interval

A er adjustment, **LPV/r treatment was not associated with an increase proporon of deleted mtDNA a er one year of PrEP.**

Photo credit:Shu erstock