MITOCHONDRIA, RENAL TUBULES AND HIV

Ryan SAMUELS[1], Carla ROCA, John SAYER, Ashley PRICE, and Brendan PAYNE

[1]Medical Student, Newcastle University

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wellcome trust centre for Mitochondrial Research

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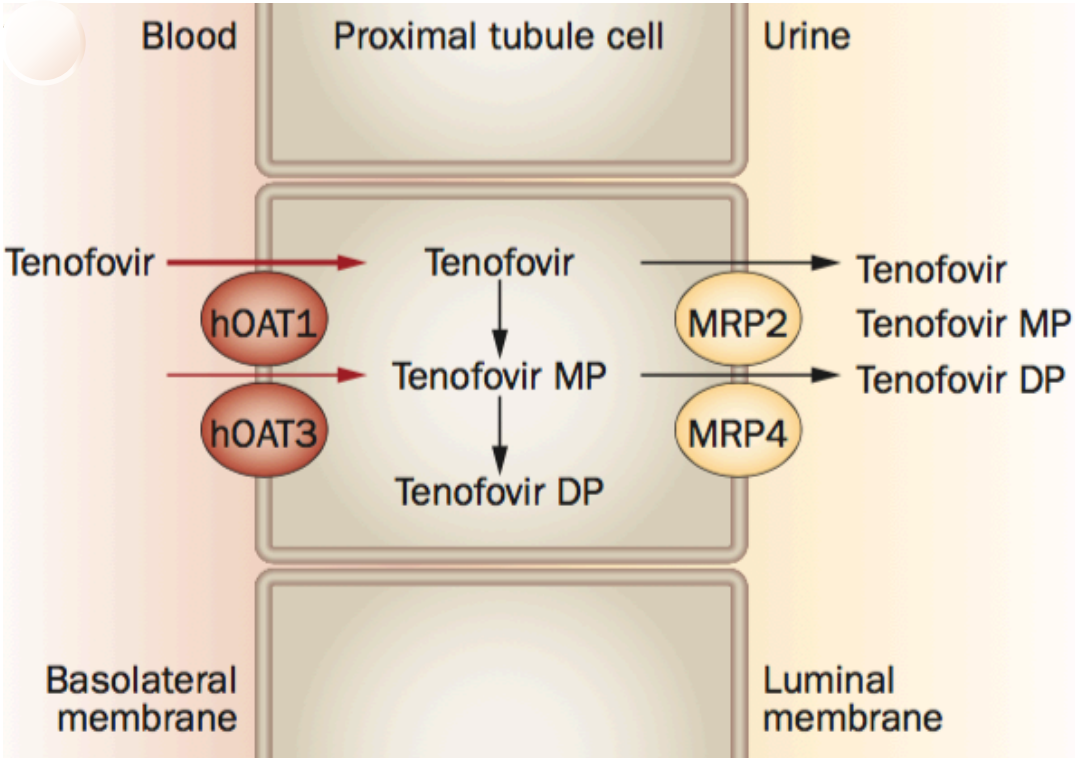
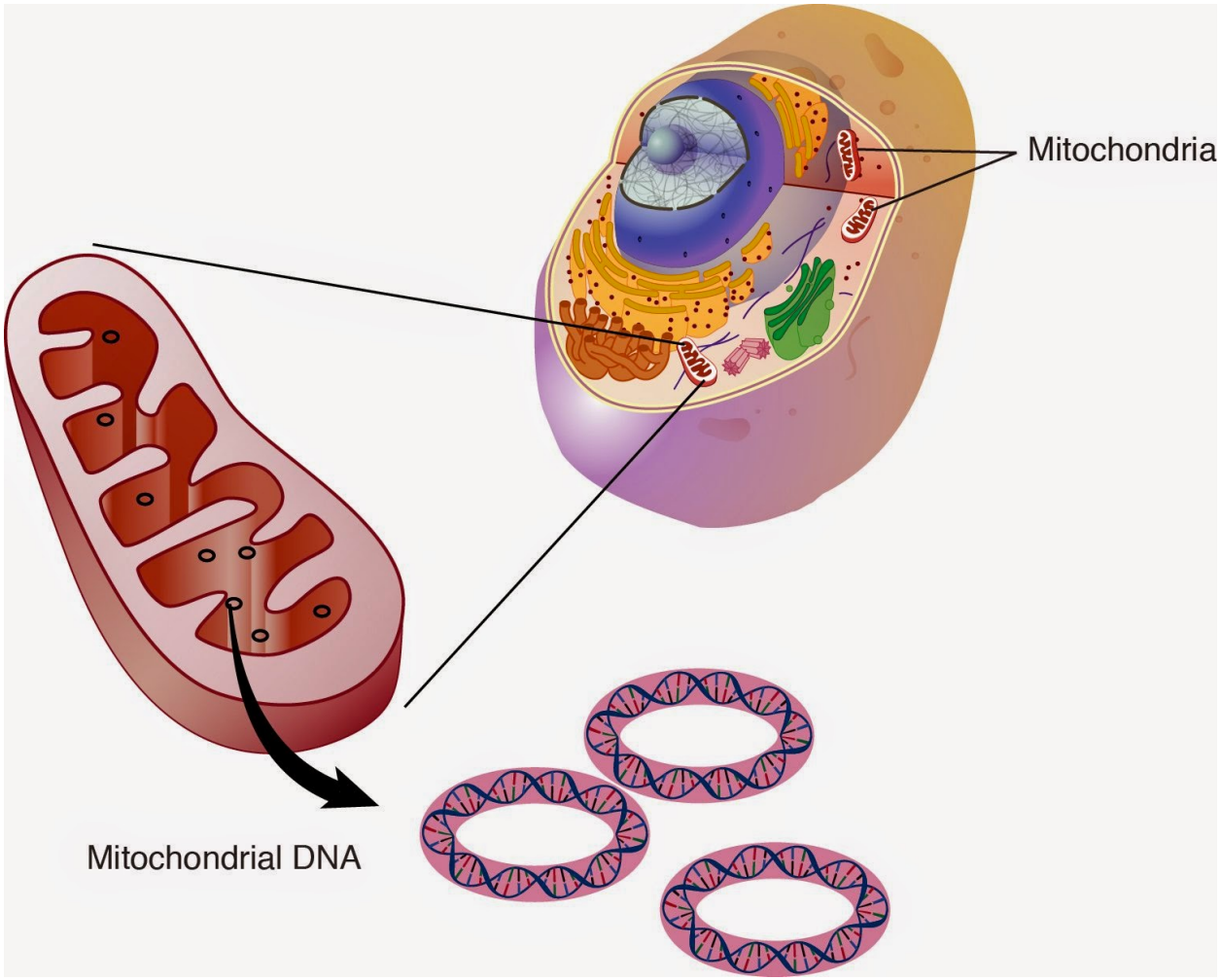
TDF in renal tubules

- Tenofovir is a common first-line anti-retroviral drug.
- May have specific toxicity in renal tubular cells.
- May cause a proximal tubulopathy.



Taken from Izzedine H, et al. 2009

Background – mitochondrial DNA



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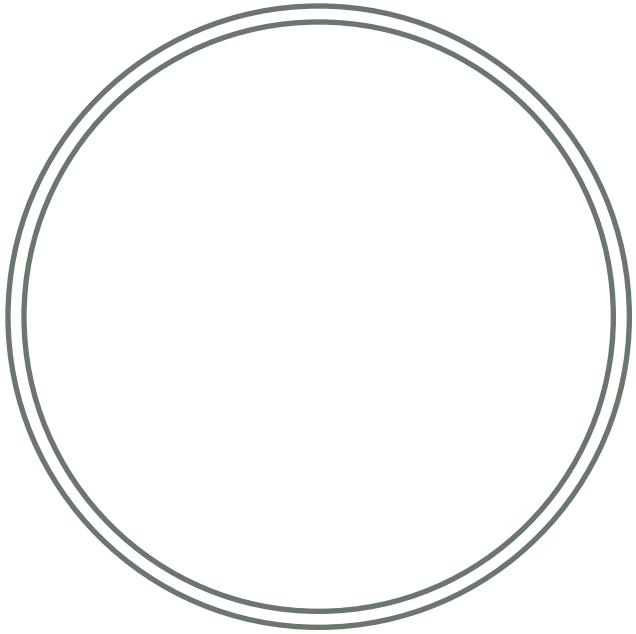
Taken from *National Institutes of Health, http://www.genome.gov/glossary/*

mtDNA Common Deletion



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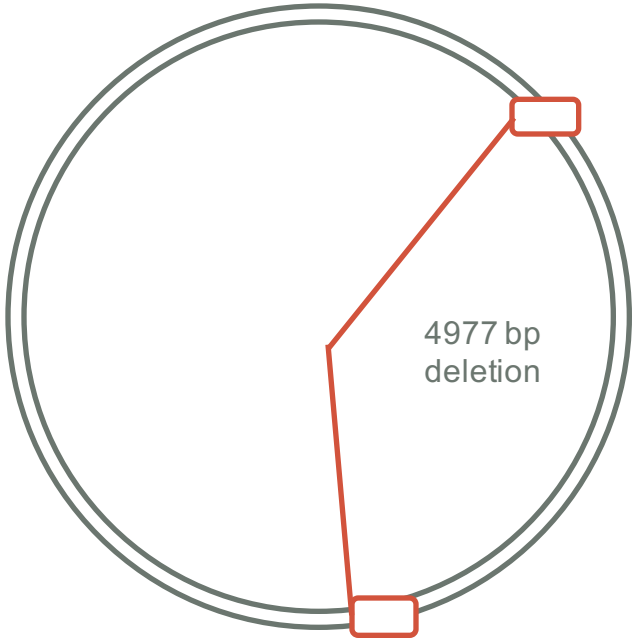

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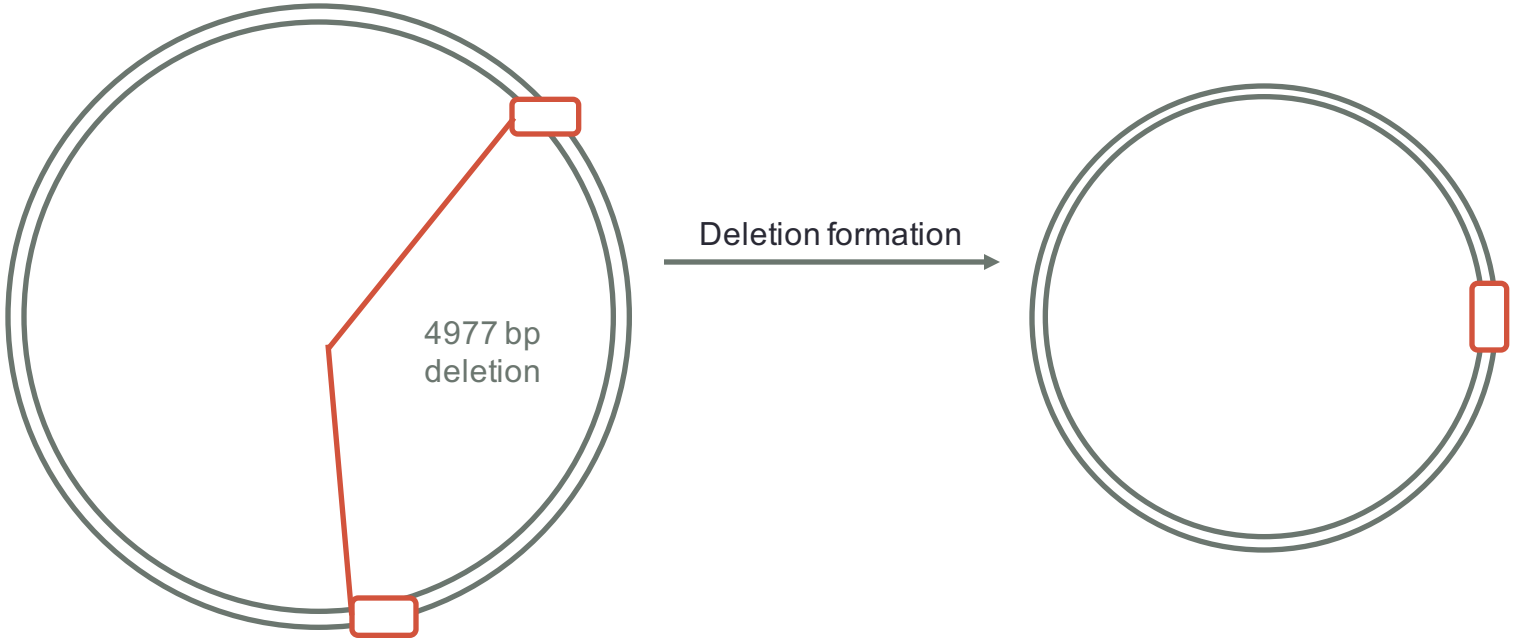

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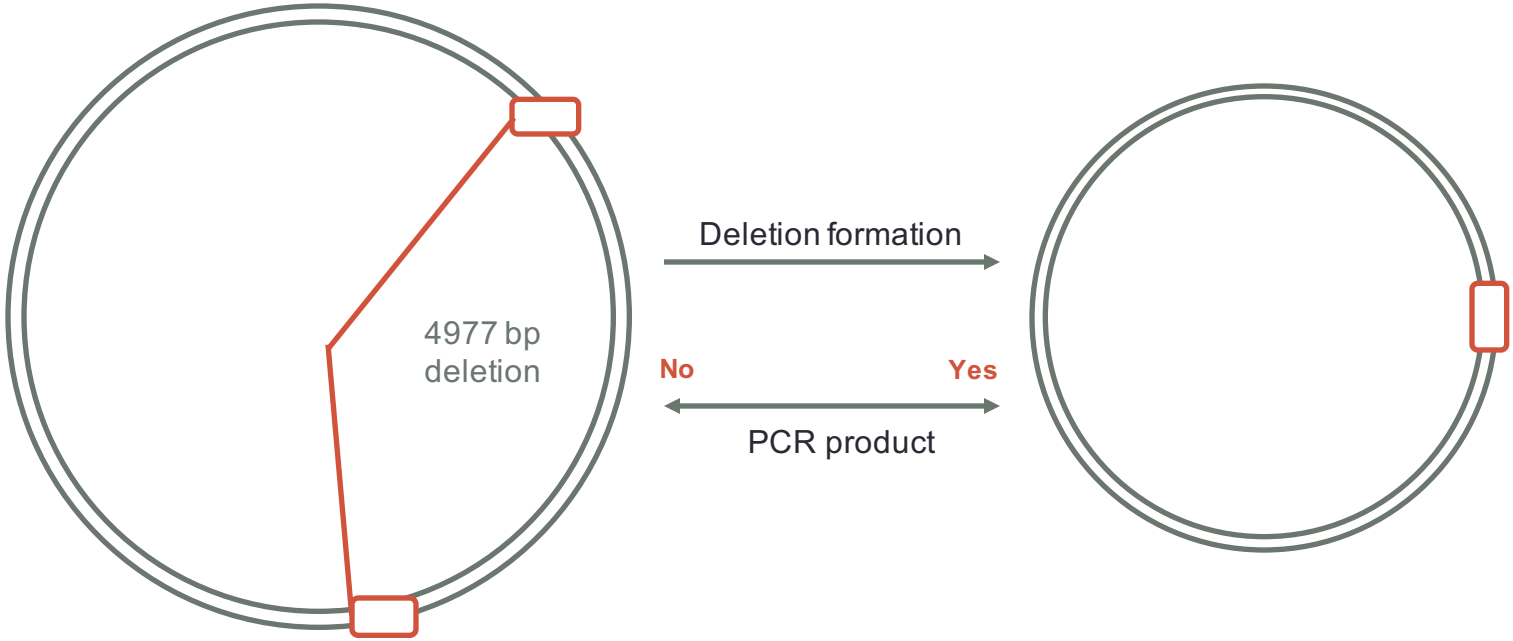

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Hypotheses

- HIV-positive, TDF-treated patients will have evidence of mtDNA damage detectable in urine
- This will correlate with proximal tubular dysfunction

Group characteristics

	Tenofovir ART (24)	Non-Tenofovir ART (11)	ART Naive (13)
Age (y)	45.3 (±10.3)	46.6 (±14.3)	36.5 (±11.7)
Male	16 (67%)	7 (64%)	12 (92%)
Time since HIV Diagnosis (months)	149 (±72)	204 (±110)	18 (±23)
Time on Treatment (months)	117 (±53)	161 (±96)	-
Current CD4 Count (cells/μL)	637 (±337)	570 (±237)	464 (±251)
HIV-1 RNA viral load (<50 c/mL)	23 (96%)	8 (73%)	-
Nadir CD4 Count (cells/μL)	135 (±98)	172 (±112)	410 (±230)
Black African ethnicity	8 (33%)	3 (27%)	0
Current smokers	7 (29%)	3 (27%)	5 (39%)

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Biochemical Data

	Tenofovir ART (24)	Non-Tenofovir ART (11)	ART Naive (13)
eGFR (CKD-EPI)	93 ±21	93 ±21	101 ±18
Renal tubular function:			
FEUa (%)	9.1 ±3.3	8.3 ±5.3	8.7 ±6.6
UPCR (mg/mmol)*	11.5 ±4.1	13.8 ±8.4	14.9 ±11.2
RBP (mg/L)	0.6 ±2.1	0	0
TmP/GFR (mmol/L)	0.82 ±0.28	1.03 ±0.30	1.02 ±0.23
Tubular dysfunction	8/22 (36%)	0/10 (0%)	2/11 (18%)

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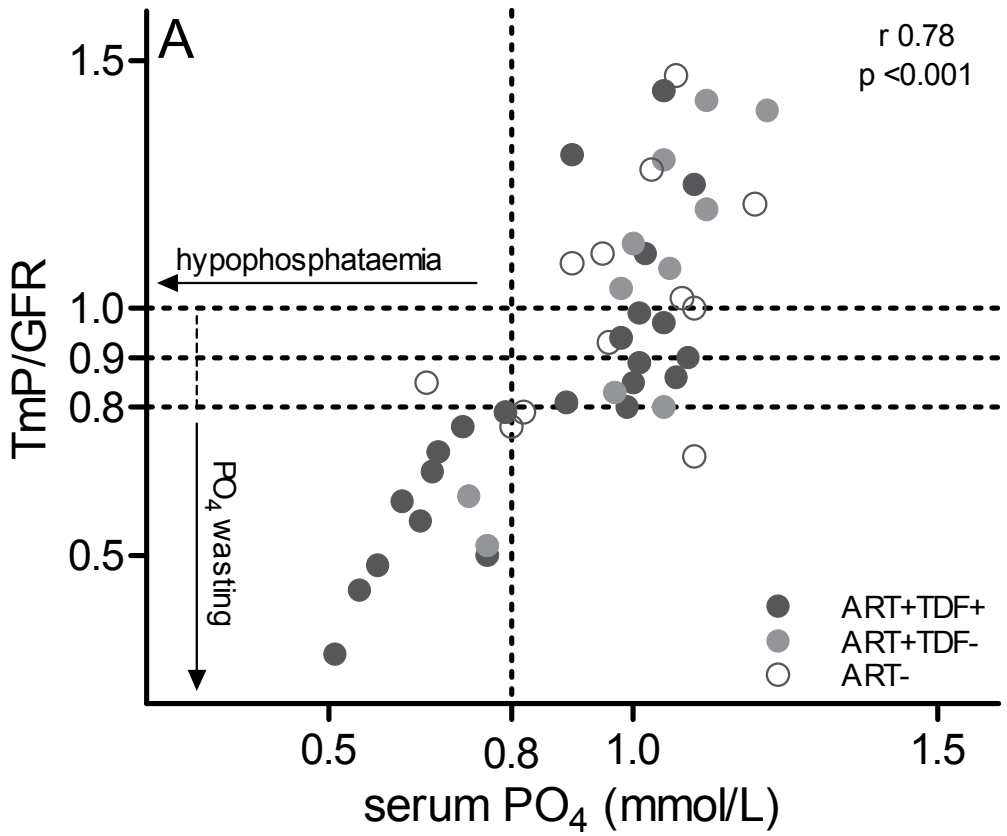
TmP/GFR



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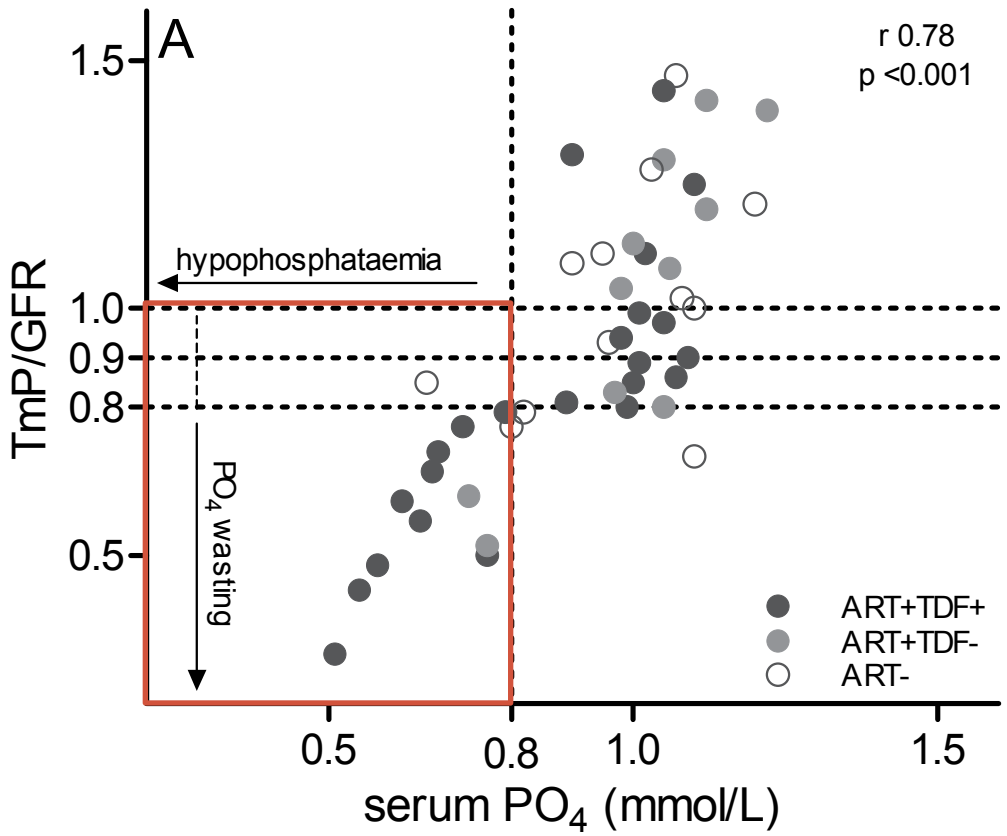
TmP/GFR



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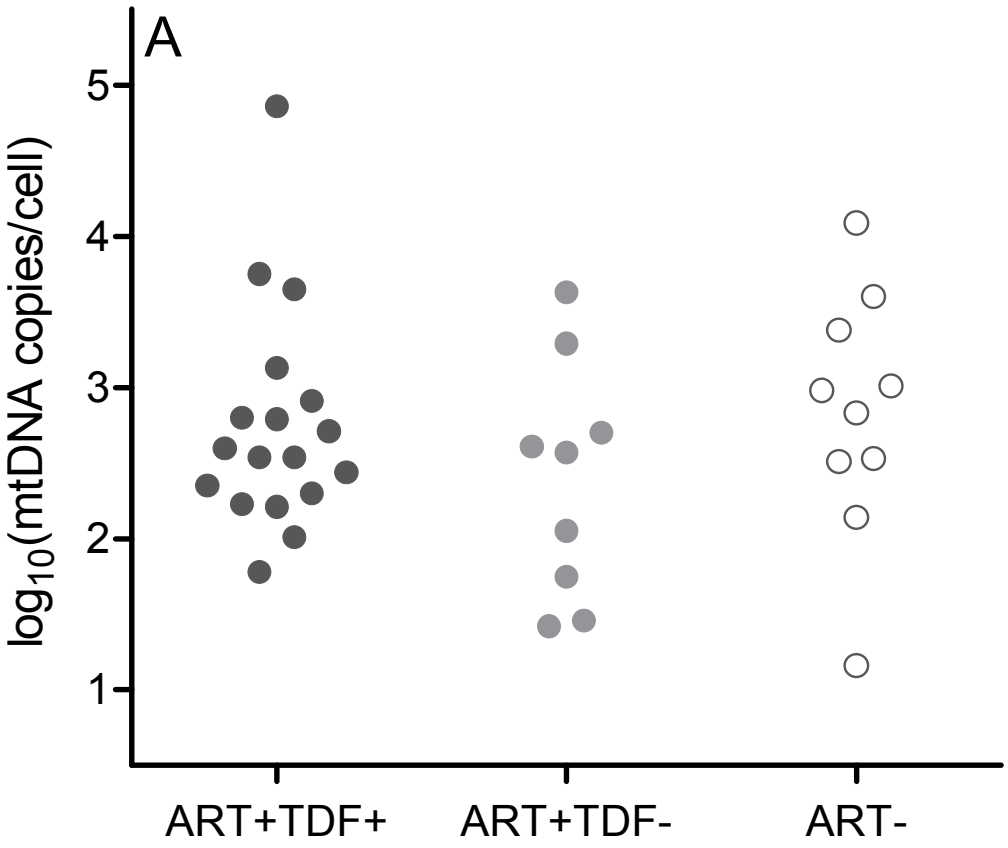
mtDNA copy number



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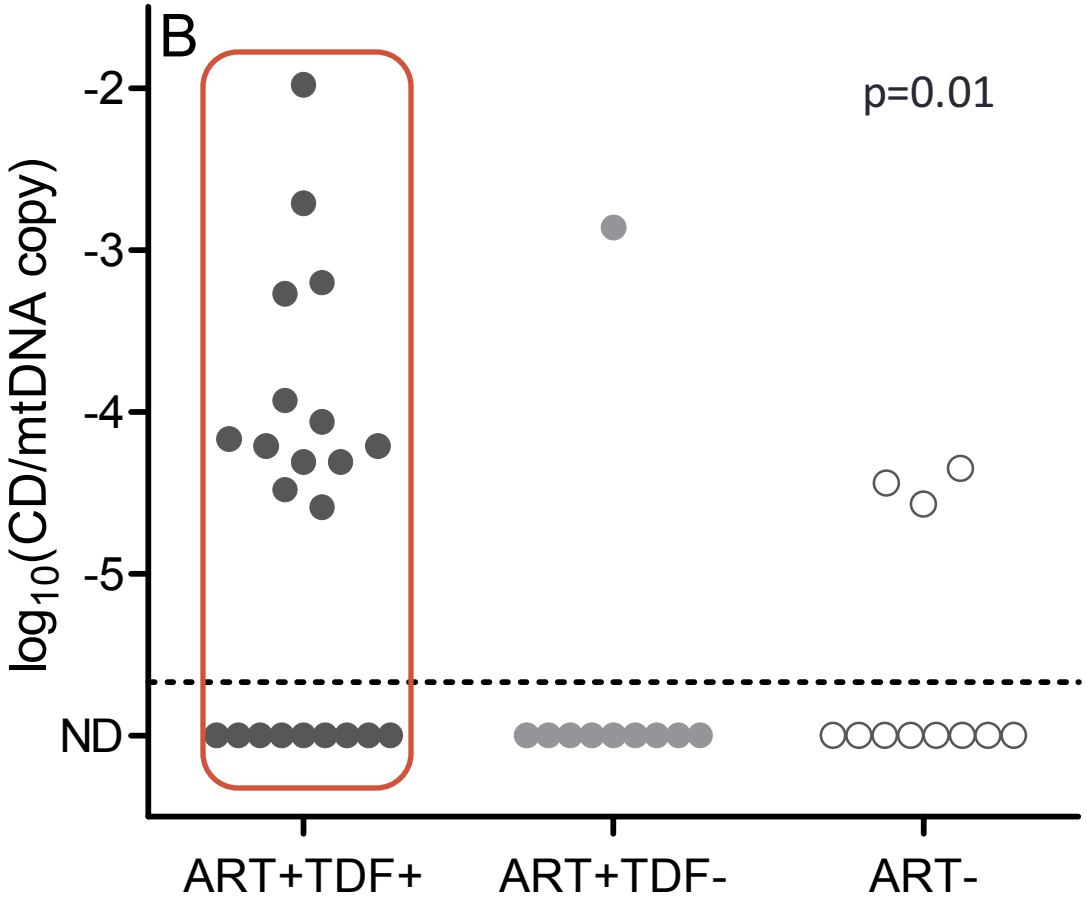
mtDNA common deletion



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Correlates of the common deletion

- mtDNA mutation detection correlated with:
  - Duration of TDF (p=0.02)
  - Tubular dysfunction (p=0.07)
  - Nadir CD4 count (p=0.07)

- Did not correlate with:
  - Age
  - Past exposure to mtDNA toxic NRTIs
    - (AZT, ddI, ddC, d4T)

Conclusions

- Urine mtDNA measurement is feasible in a clinical setting
- mtDNA mutations in urine correlate with TDF exposure

Limitations / future work

- Larger study
- Longitudinal changes: do they predict tubulopathy?
- Does this define an ‘at risk’ subgroup within TDF treated patients?
- Define mtDNA changes in specific cell types

Acknowledgements

- Brendan Payne
- Carla Roca
- Ashley Price
- John Sayer

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BIA British Infection Association

Thank you!

Any questions?