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Imperial College London

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Impact of maraviroc-intensification on immunisation and T-cell activation: *A phase IV randomised double-blinded placebo-controlled study*

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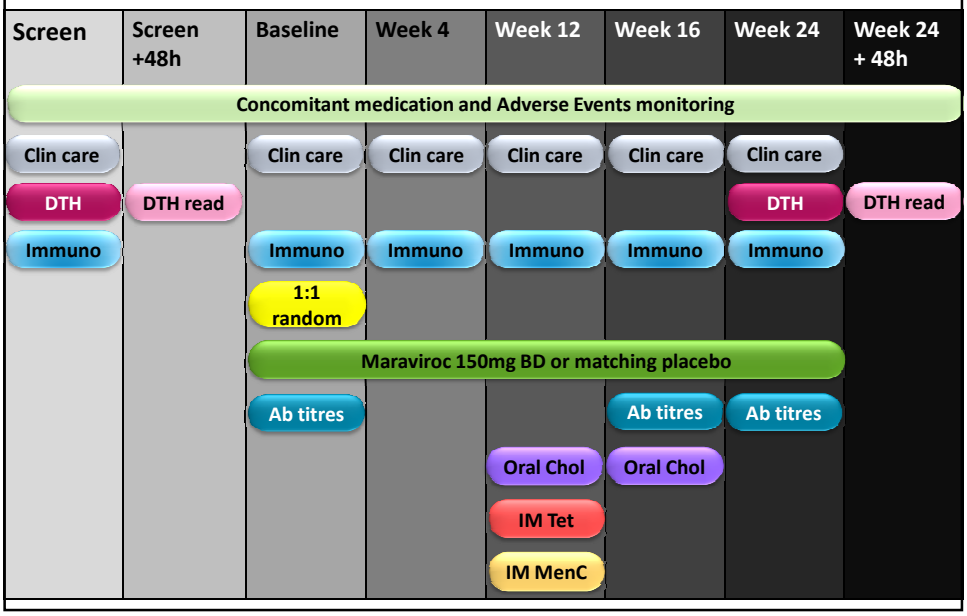
Objectives

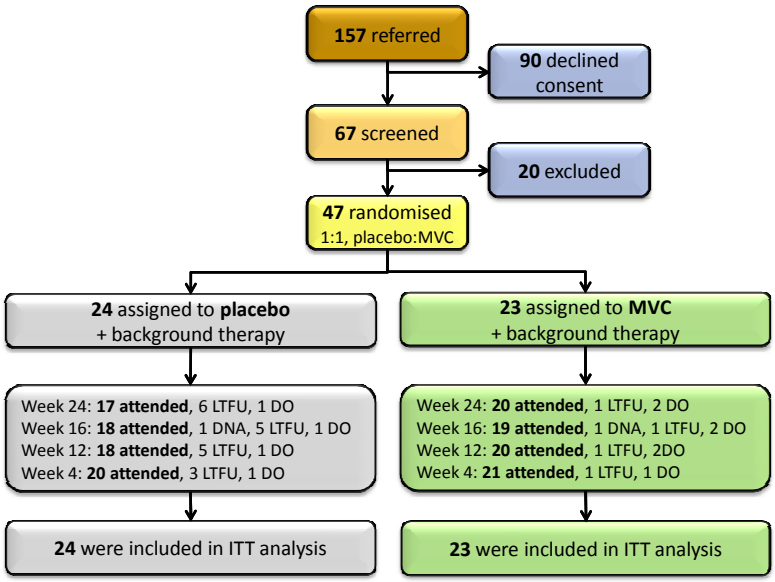
- HIV-1 entry blockade by CCR5-antagonists potentiates **immunomodulation**.

- We hypothesised that maraviroc-intensification favourably impacts
  - Response to **immunisation**
  - T-cell **phenotype** and **function**
  - Delayed-type hypersensitivity (**DTH**) in HIV-1^{+} subjects.

Study Design



Referral, Screening and Randomisation



Methods

- Clinical Care
- Delayed Type Hypersensitivity; Mantoux skin test
- Detailed Immunology
  - *T-cell Phenotype; surface markers of differentiation, activation, senescence, exhaustion, co-stimulation and co-inhibition*
  - *T-cell Function; IFN-γ, IL-2, perforin and proliferation in response to HIV-1 Gag peptides, CMV and TTox*
  - *Humoral Immunity; anti-tetanus, -MenC and -cholera antibody titres*

Methods

- Statistical Methods
  - *Linear mixed model (SAS v9.1.3) compared between group data collected over time to derive time-weighted differences from baseline to each time-point.*
  - *Point estimates and 95% CI of changes from baseline are presented.*

Adverse Events and Clinical Parameters

	Oral MVC	System	Placebo	System
Grade 1 & 2	**49**		**36**	
Possibly	*8*	*GI, CNS, MS,*	*4*	*GI, CNS, Skin*
Probably	*1*	*Psych, ENT*	*0*	
Definitely	*0*		*1*	
Grade 3	**0**		**1**	
Possibly	*0*	-	*1*	*GI*
Probably	*0*		*0*	
Definitely	*0*		*0*	

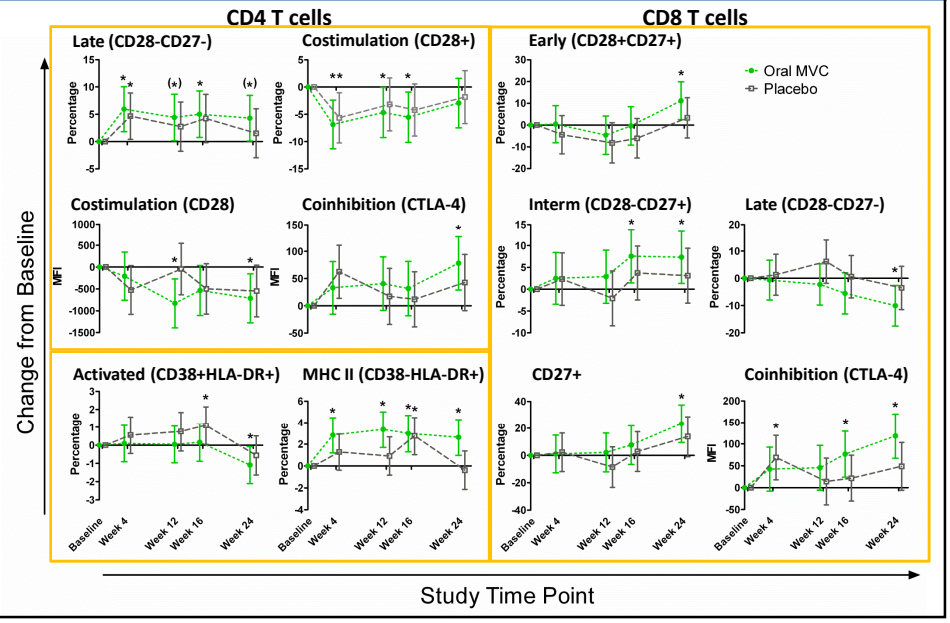
No clinically relevant changes in:

- Lymphocyte subsets
- Viral load
- Haematology
- Biochemistry

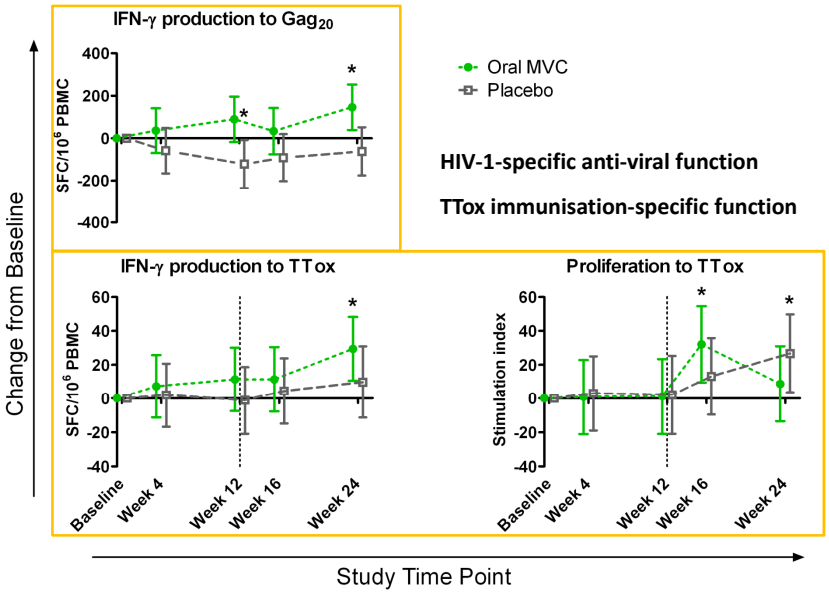
Delayed Type Hypersensitivity

	Oral MVC n=23	Placebo n=24	p-value
Pre baseline reaction results (%)			
Negative (< 5mm induration)	22 (95.7)	21 (87.5)	0.632
Positive (= 5mm induration)	1 (4.4)	3 (12.5)	
Week 24 reaction results (%)			
Negative (< 5mm induration)	15 (75.0)	11 (64.7)	0.909
Positive (= 5mm induration)	0 (0.0)	1 (5.9)	
Not known	5 (25.0)	5 (29.4)	
Not applicable as not administered	3	7	
Agreement baseline to week 24			
κ	**100%**	**100%**	**-**
(95%CI)	**(78-100)**	**(74-100)**	

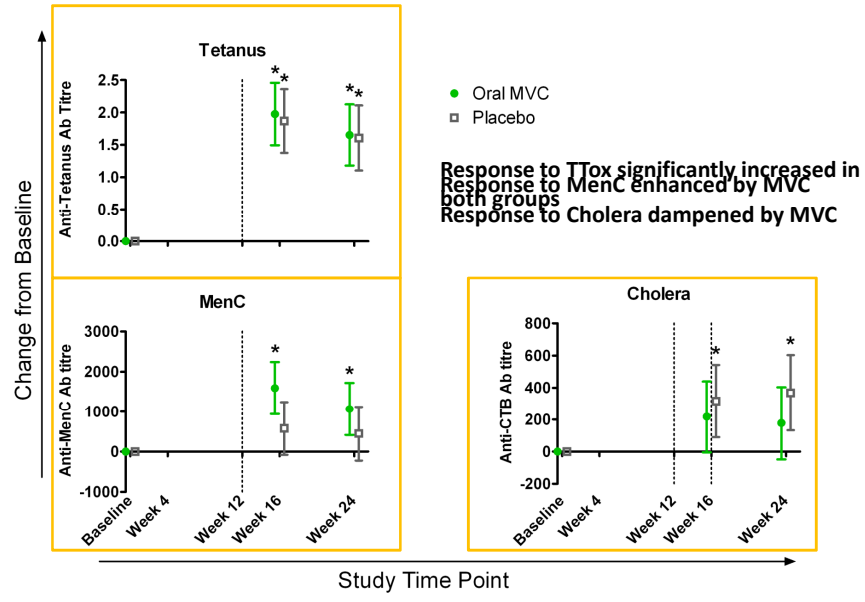
T-cell Phenotype



T-cell Function



Humoral Responses to Immunisation



Summary

- No excess of AE or clinically relevant changes (VL, LSS, Chem, Haem)
- No change in DTH
- **Reduced CD4 T-cell activation**
- Increased number of MHC-II expressing and late-stage CD4 T cells
- **Normalisation of CD8 T-cell skewing** towards early and intermediate
- Less expression of co-stimulatory and more co-inhibitory molecules
- **Improved anti-Gag and anti-Ttox T-cell function** and expedited proliferation to Tetanus boost
- **Enhanced humoral neo-response** to MenC immunisation, however **reduced humoral neo-response** to Cholera immunisation
- **No effect on recall humoral response** to Tetanus boost

Conclusion

Maraviroc-intensification favourably influences immune profiles of HIV-1^{+} patients, supporting immunomodulatory use in HIV-1 infection and potentially other immunologically relevant settings.

Acknowledgements

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Imperial College London

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