Modulation of monocyte phenotypes and cytokine responses in low-risk gbMSM taking HIV pre-exposure prophylaxis

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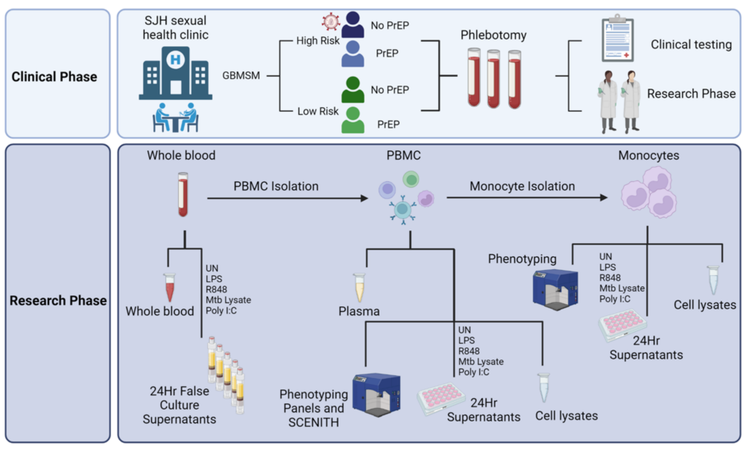
INTRODUCTION

Certain sexual practices, such as condomless anal sex, remain a significant risk for HIV acquisition amongst gay, bisexual and other men who have sex with men (gbMSM). HIV pre-exposure prophylaxis (PrEP) in the form of two anti-retroviral agents (TDF and FTC) reduces HIV acquisition risk. In these individuals it is likely that ongoing intermittent HIV exposure leads to an immune response dictated by the innate immune system, partly aborted by PrEP, preventing a mature adaptive response. Innate immune responses to HIV and to other stimuli in PrEP are under-studied. Prior cytokine work in monocytes from PrEP participants demonstrated increased IL-17 and TNFα production, suggesting innate immune differences. TDF has demonstrated effects on the host immune response, with reduced LPS-mediated IL-10 production, enhanced type III interferon levels and ISG expression. This suggests that PrEP may have immunomodulatory effects, independent of HIV exposure.

METHODS



Low-risk gbMSM, as defined by ≤5 condomless partners in six months, were recruited through the St James's Hospital PrEP service. This included individuals currently taking PrEP and those who were due to commence PrEP. Social, demographic, and sexual health factors were recorded. Peripheral blood mononuclear cells were isolated from whole blood, with subsequent monocyte isolation. Monocyte phenotypes were analysed via flow cytometry, and monocyte cytokine production was assessed by Luminex Multiplex ELISA under unstimulated conditions as well as after stimulation with R848 (TLR7/TLR8 agonist) and Mycobacterial tuberculosis (pan-activation receptor agonist). Cytokines measured included MIP1α, MIP1β, TNFα, IL-10, IL-1α, IL-1β, IFNγ, IFNα, GCSF and GMCSF.

CONCLUSION

In low-risk individuals taking PrEP, there was evidence of increased monocyte activation compared to similar non-PrEP individuals. Monocytes in individuals receiving PrEP demonstrate defective responses to TLR7 and TLR8 stimulation. These defects can be overcome by co-stimulation of other TLRs. This work suggests that PrEP has direct immunomodulatory effects independent of exposure risk.

RESULTS

N=17 gbMSM were recruited (n=10 not on PrEP, n=7 taking PrEP) (**Table 1**). The median time on PrEP in the n=7 PrEP cohort was 463 days (IQR 441 – 1416). Taking PrEP was associated with increased CD14 expression on monocytes (**Fig 1E**), while there were no differences in lymphocyte populations (**Fig 2**). Under unstimulated conditions, PrEP was associated with reduced monocyte GMCSF production (data not shown). Following stimulation with R848, PrEP use was associated with reduced production of MIP1α, MIP1β, IL-10, IL-1α, GCSF and GMCSF (**Fig 3, Fig 4**). Following stimulation of other TLRs, these differences were overcome, while PrEP use was associated with increased GMCSF production (**Fig 5**).

	Whole cohort N=17	Low risk, no PrEP N=10	Low risk, taking PrEP N=7	
Age, years; mean (SD)	33.5 (8.3)	34.3 (2.8)	32.4 (3.1)	t=0.45, p=0.66
Ethnicity, n (%)				X^2=2.55, p=0.64
- White Irish	4 ()	2 ()	2 ()	
- White European	6 ()	3 ()	3 ()	
- Other white	4 ()	2 ()	2 ()	
- East Asian	1 ()	1 ()	0 (0)	
- Other Asian	2 ()	2 ()	0 (0)	
Partners in last six months, n; mean (SD)	6 (4)	6 (4)	7 (5)	t=-0.60 p=0.56
Condom use, n				X^2=3.40, p=0.34
- always	7	5	2	
- >50%	5	3	2	
- <50%	2	0	2	
- never	3	2	1	

Figure 3

Figure 1

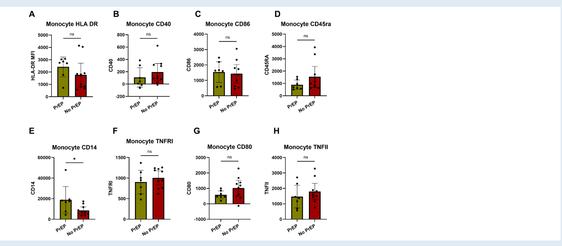


Figure 2

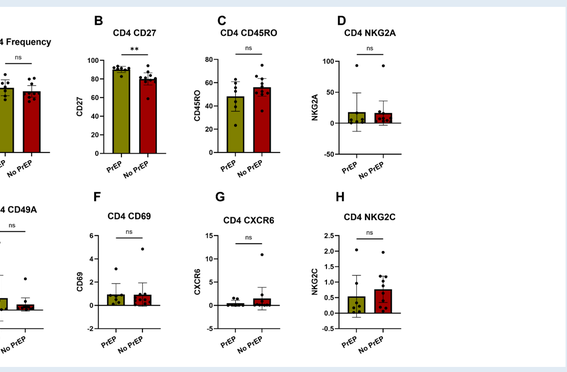


Figure 4

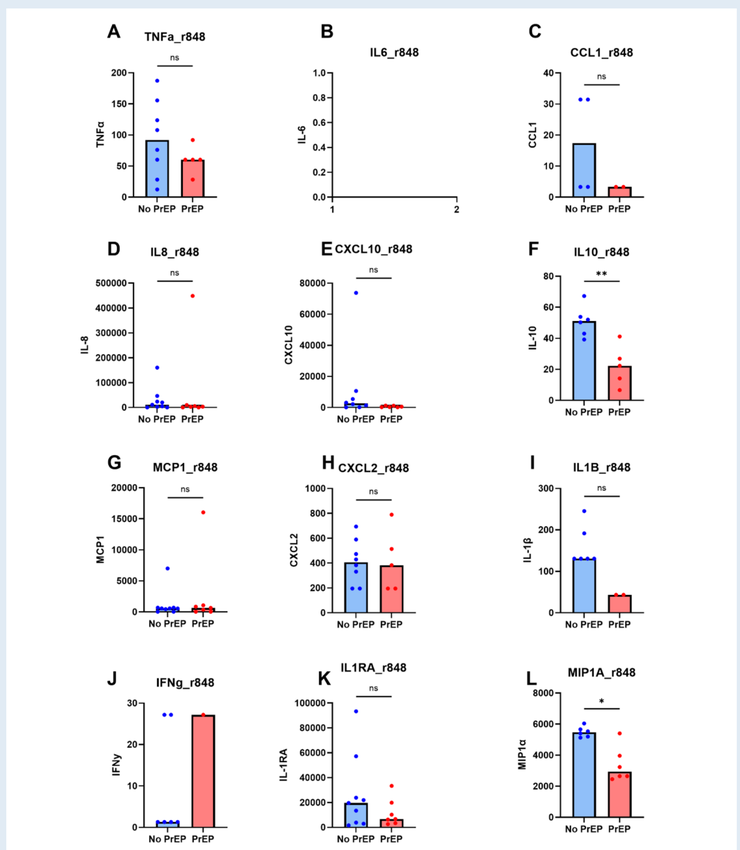


Figure 5

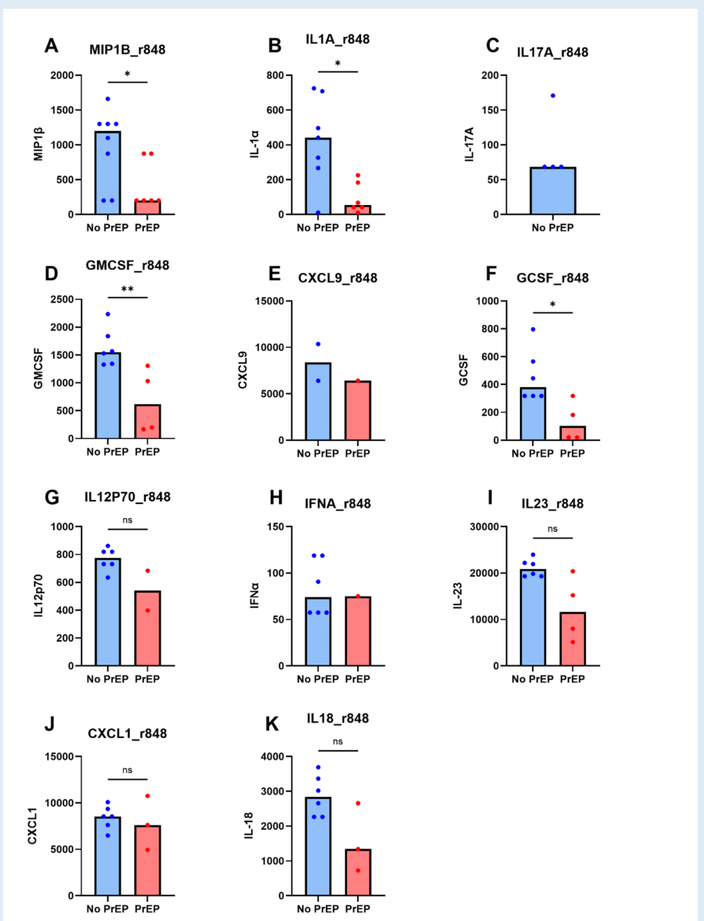
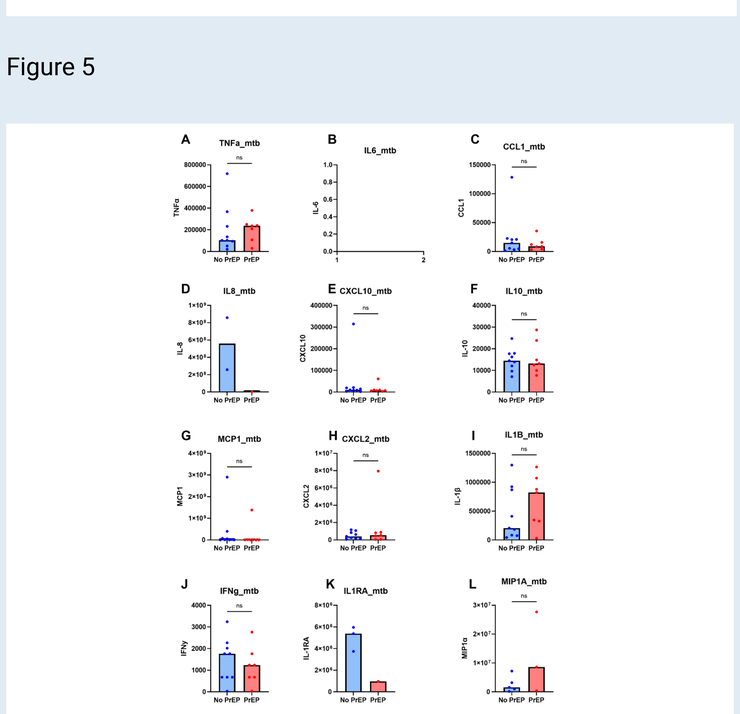
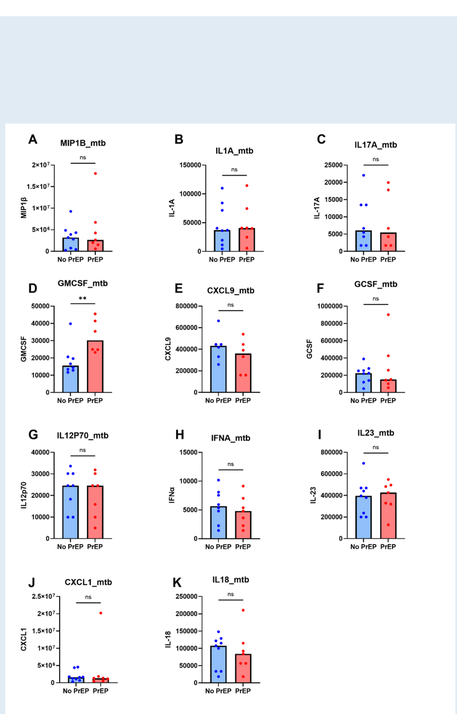


Figure 6





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