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Therapeutic immunisation in conjunction with IL-2, GM-CSF and rhGH improves CD4 T-cell counts and reduces immune activation in cART-treated HIV-1^{+} patients: a phase I clinical study

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Immunotherapy and HIV-1

- Combination antiretroviral therapy (cART) in the context of HIV-1 infection
  - controls viral replication and leads to an increase in CD4 T-cell count
- Immune defects persist
  - T-cell numbers in the gut are not fully recovered
  - therapy interruption leads to a rapid rebound in HIV-1 viraemia
  - abnormal levels of immune activation and inflammation persist
  - HIV-1-specifc T-cell functionality is not fully recovered
  - viral reservoirs persist – in central and transitional memory CD4 T cells
- Immune-based therapy (IBT) in treated, chronic HIV-1 infection
  - aims to improve the immune system to control the virus
  - there is the potential for IBT to improve HIV-1-specific T-cell responses and deplete viral reservoirs

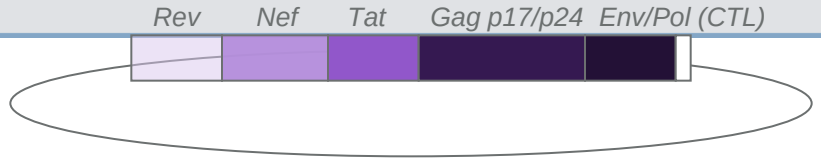
Study design

Week	Screen X 2	0	1 Days 8-12	2 Days 14-18	4	6	8	12	16	24	48
Arm 1 n = 3		FIT Vaccine	IL-2 + GM-CSF	rhGH		FIT Vaccine		FIT Vaccine			
Arm 2 n = 4		FIT Vaccine				FIT Vaccine		FIT Vaccine			
Arm 3 n = 5			IL-2 + GM-CSF	rhGH							

Dosage information:

- FIT Biotech DNA clade B vaccine 1mg/ml, 10 x 100µl intradermal injections
- IL-2 5 x 10^6 Units subcutaneously, twice a day, eight hours apart
- GM-CSF 150µg subcutaneously, once daily, four hours from the IL-2
- rhGH 4mg/day subcutaneously, once daily

Study drugs and timing of administration



- DNA clade B vaccine (FIT Biotech)
  - therapeutic vaccines aim to induce the recovery of HIV-1-specific responses
    - » plasmids contained structural and regulatory HIV-1 genes
    - » elicit both CD4 and CD8 T-cell responses against the proteins that these genes encode
- Interleukin-2 (IL-2)
  - induces T-cell proliferation
  - increases CD4 T-cell numbers (in the context of HIV-1 infection)
    - » although no long-term clinical benefits have been reported
  - IL-2 given during the antigen-specific T-cell contraction phase
    - » preserves and maintains clinically relevant responses
    - » in this study IL-2 was administered following therapeutic immunisation

Aim: to enhance and sustain the response following antigenic stimulation

Study drugs and timing of administration

- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
  - allows further immune reconstitution in the periphery
    - » improves antigen presentation by cells of the monocytic lineage to generate fully functional HIV-1-specific CD4 and CD8 T-cell responses
- Recombinant human growth hormone (rhGH)
  - has been used to treat HIV-1-associated lipodystrophy
    - » increase thymic activity/output
    - » reduce immune activation
    - » enhance HIV-1-specific T-cell responses

Overall aim: to steer the immune system away from an anergic/unresponsive profile, to increase the naïve T-cell pool, and to control/eradicate the virus

Eligibility criteria

Randomised, open-label, phase I immunotherapeutic study

- Chronically infected with HIV-1
- On stable long-term cART
- Undetectable plasma viral load (<50 copies/ml)
- CD4 T-cell count >400 cells/mm^3
- Not receiving nor have received immunomodulatory drugs or immunisation

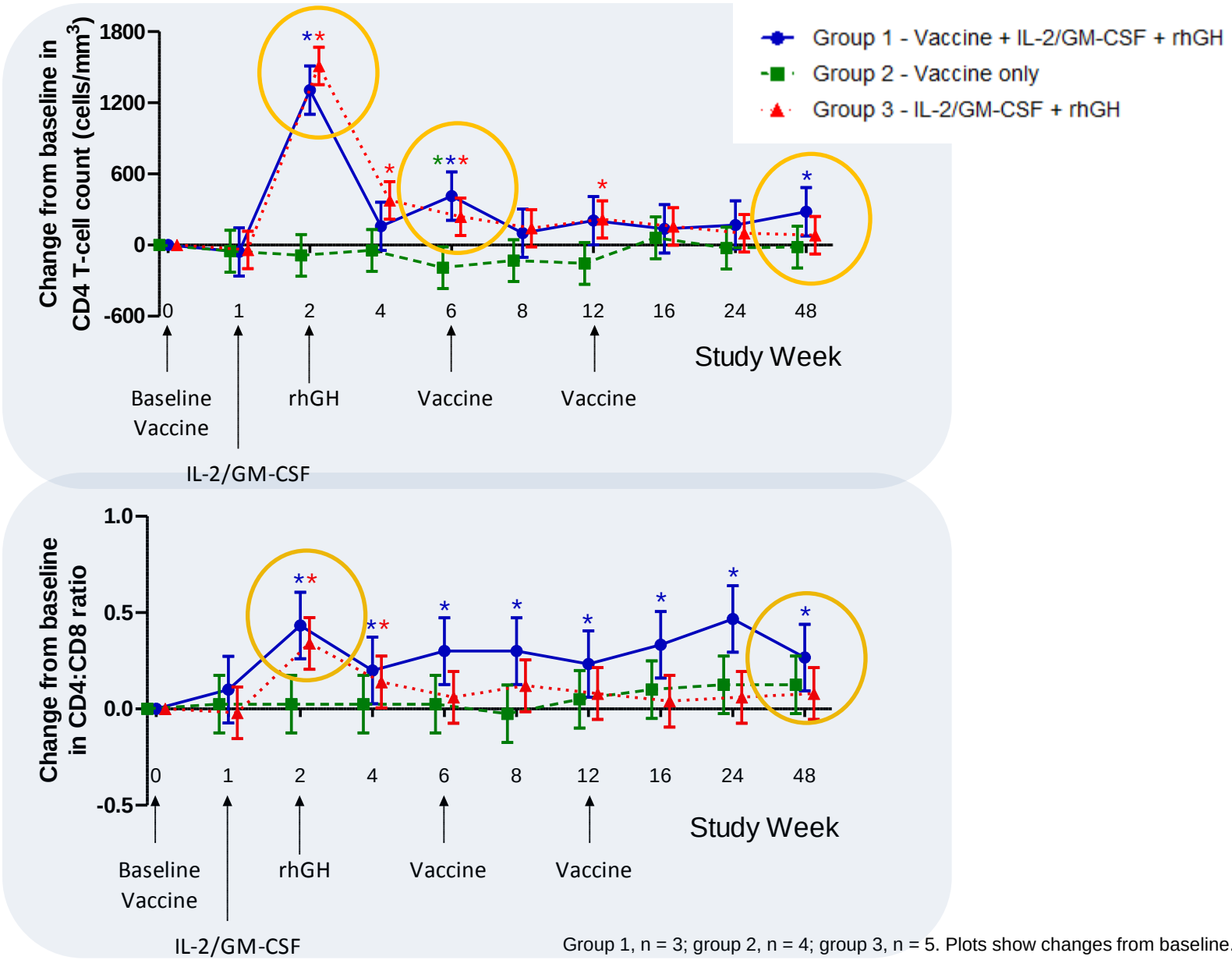
Out of 93 patient referrals and 21 screen visits, 12 patients that met the eligibility criteria were enrolled onto the trial

Baseline patient characteristics

Patient short code	Group	Graph symbol	Age (years)	Gender	Clade of infection	Length of time since diagnosis (months)	Duration of cART (months)	cART regimen	CD4 T-cell count (cells/mm³)		Plasma viral load at baseline (copies/ml)
									Nadir	Baseline	
R771	1	●	64	M	B	160.13	139.05	FTC+TFV+EFV	391	884	<50
B784	1	●	40	M	B	99.25	98.95	FTC+TFV+EFV	80	1332	<50
G739	1	●	43	M	B	141.61	113.15	FTC+TFV+EFV	227	534	<50
P087	2	■	50	M	B	172.95	162.75	FTC+TFV+EFV	210	731	<50
C789	2	■	29	M	B	20.75	12.20	FTC+TFV+EFV	309	535	<50
L043	2	■	47	M	B	90.69	45.87	FTC+TFV+EFV	303	782	<50
C319	2	■	48	M	B	229.05	80.03	FTC+TFV+ETV	93	1077	<50
F810	3	▲	50	M	B	233.41	193.54	FTC+TFV+NVP	166	582	<50
O523	3	▲	53	F	C	84.10	62.89	FTC+TFV+ETR	284	892	<50
S648	3	▲	52	M	B	300.39	158.43	TFV+DRV+RTV	227	578	<50
C241	3	▲	47	M	B	144.23	87.18	FTC+TFV+DRV+ RTV	180	466	<50
P054	3	▲	33	M	B	40.80	28.80	FTC+TFV+EFV	200	840	<50
		Median	48			142.92	93.07		219	757	
		IQR	42-51			89.04-186.98	58.63-143.89		177-289	567-886	

IQR – interquartile range; FTC – emtricitabine; TFV – tenofovir; EFV – efavirenz; NVP – nevirapine; ETR – etravirine; DRV – darunavir; RTV – ritonavir.

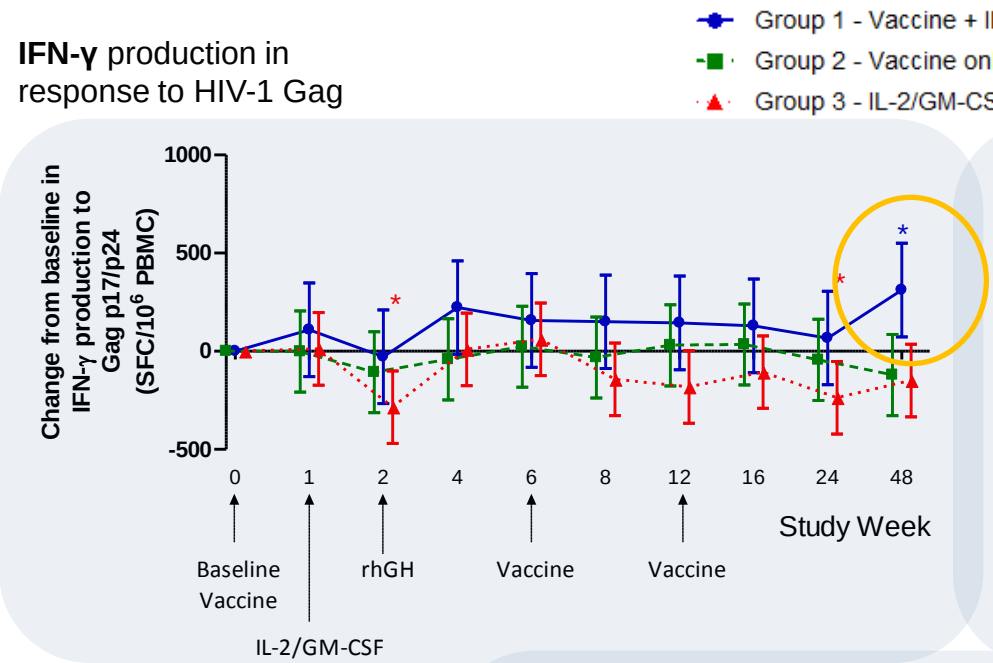
Changes in CD4 T-cell count and ratio



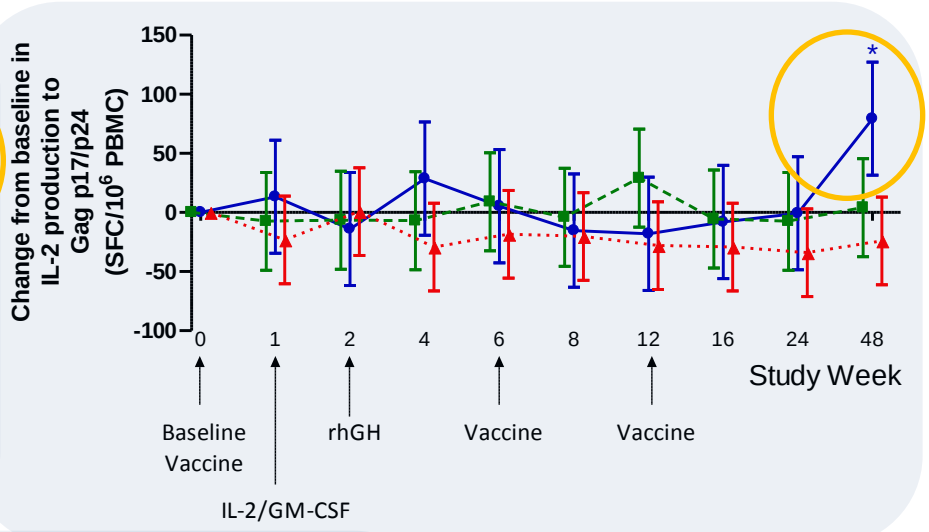
Group 1, n = 3; group 2, n = 4; group 3, n = 5. Plots show changes from baseline.

Changes in T-cell function

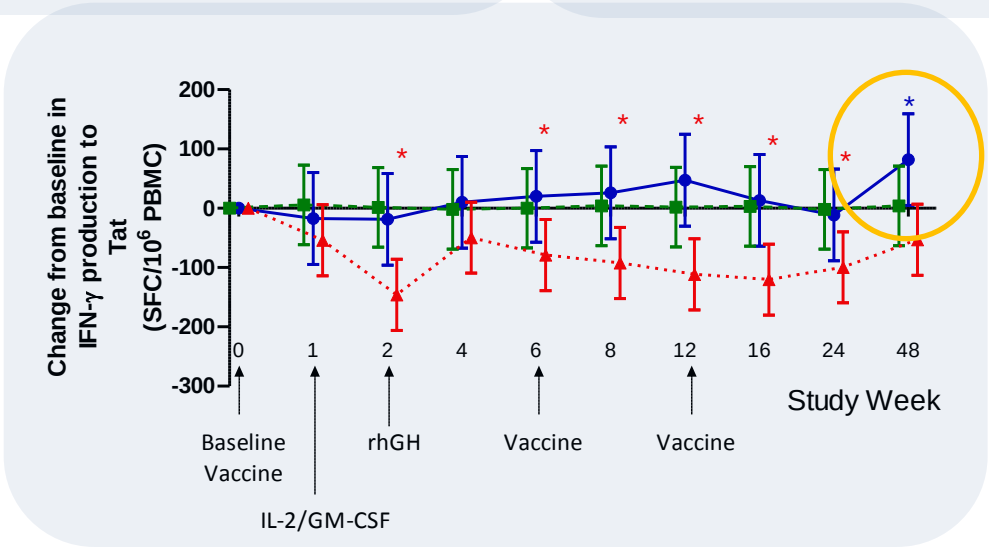
IFN-γ production in response to HIV-1 Gag



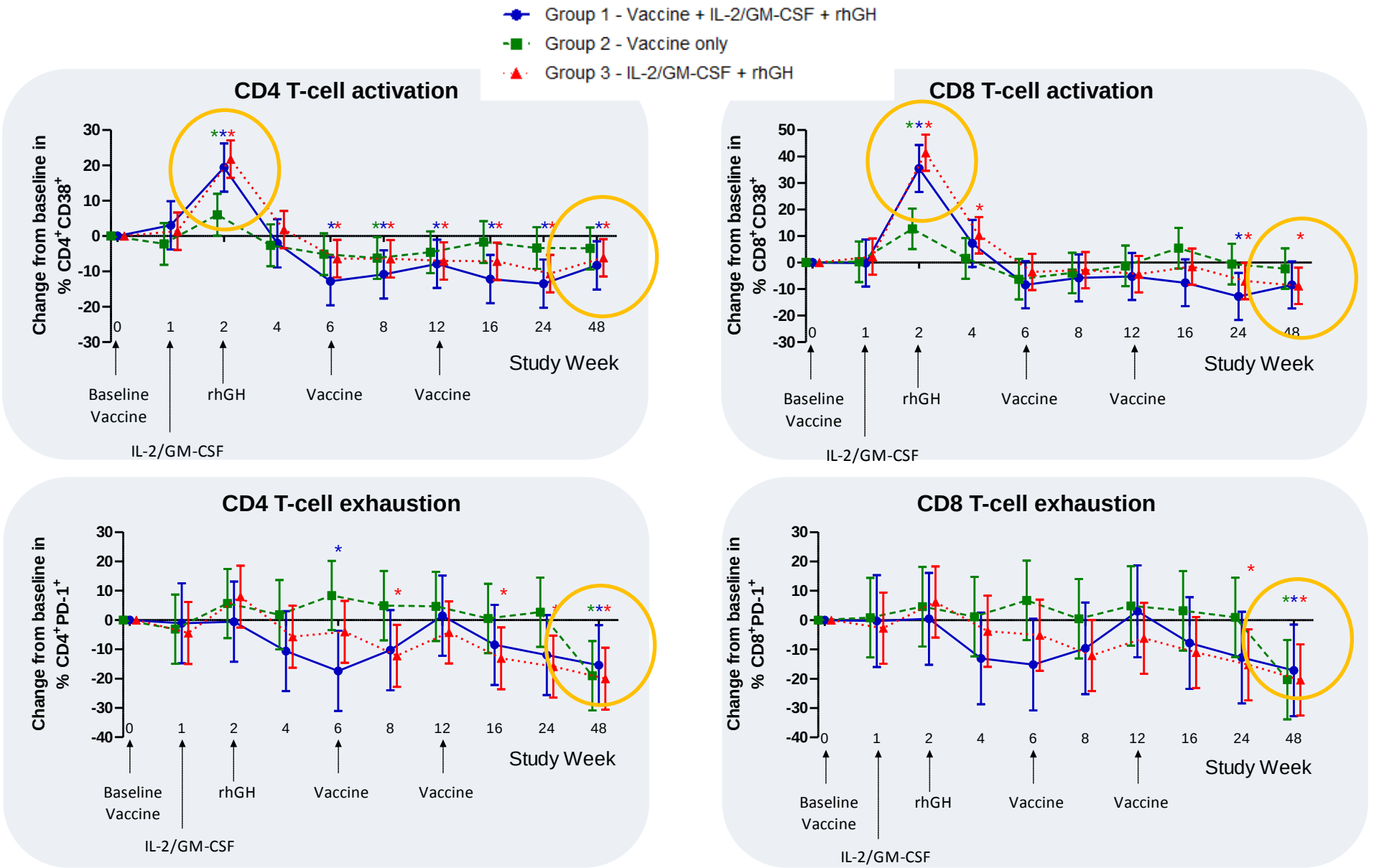
IL-2 production in response to HIV-1 Gag



IFN-γ production in response to HIV-1 Tat



Changes in T-cell phenotype



Summary

- Minor blips in HIV-1 plasma viral load occurred
  - could not be attributed to a particular treatment group or study time point
  - the majority were <100 copies/ml and all undetectable at week 48
- Overall, the study drugs were well-tolerated
- Patients in all study groups showed reductions in PD-1 expression at week 48, indicating a reversal of the exhausted T-cell phenotype
  - potentially an effect of an additional 48 weeks cART
- Patients in **group 1** (received vaccine, IL-2, GM-CSF, rhGH) showed:
  - increased numbers of CD4 T cells
  - improved CD4/CD8 T-cell ratios
  - increased IFN-γ production in response to HIV-1 Gag and Tat
  - increased IL-2 production in response to HIV-1 Gag
  - reduced expression of the activation marker CD38 on T cells

Future work

- Further analysis of cryopreserved samples to include:
  - quantification of HIV-1 proviral DNA
  - measurement of differentiation, activation and exhaustion markers on virus-specific T cells (using multimer technology)
  - assessment of polyfunctionality at key study time points
  - elucidation of the preservation of the functional response after 48 weeks – recall patients

Such therapeutic strategies should not only induce but maintain these benefits (increased CD4 T-cell numbers, enhanced T-cell functionality and reversal of defective immunophenotypes); ideally accompanied by a depletion of the viral reservoir

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