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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-specific 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

### 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

<table>
<thead>
<tr>
<th>Week</th>
<th>Screen X 2</th>
<th>0 (Days 8-12)</th>
<th>2 (Days 14-18)</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
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<td>Arm 1 n = 3</td>
<td>FIT Vaccine</td>
<td>IL-2 + GM-CSF</td>
<td>rhGH</td>
<td>FIT Vaccine</td>
<td>FIT Vaccine</td>
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<td>FIT Vaccine</td>
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<td>Arm 3 n = 5</td>
<td>IL-2 + GM-CSF</td>
<td>rhGH</td>
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</table>

**Notes:**
- Arm 1: FIT Vaccine, rhGH
- Arm 2: FIT Vaccine, rhGH
- Arm 3: IL-2 + GM-CSF, rhGH
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/mm³
- 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

<table>
<thead>
<tr>
<th>Patient short code</th>
<th>Group</th>
<th>Graph symbol</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Clade of infection</th>
<th>Length of time since diagnosis (months)</th>
<th>Duration of cART (months)</th>
<th>cART regimen</th>
<th>CD4 T-cell count (cells/mm³)</th>
<th>Plasma viral load at baseline (copies/ml)</th>
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<td>M</td>
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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

**CD4 T-cell activation**

- Group 1 - Vaccine + IL-2/GM-CSF + rhGH
- Group 2 - Vaccine only
- Group 3 - IL-2/GM-CSF + rhGH

**CD8 T-cell activation**

**CD4 T-cell exhaustion**

**CD8 T-cell exhaustion**

- CD4+PD-1+ T-cell exhaustion
- CD8+PD-1+ T-cell exhaustion
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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BHIVA

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