Immunological manifestations of increasing age, ART duration and time since diagnosis within the ageing HIV-1\(^+\) cohort

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The Ageing Cohort (n=6106)

- Median age in 1996-2000 = 33 years
- Increase of 8 years during 14 year follow-up period
- Median age in 2010 = 41 years

(see abstract #P118, S Mandalia et al.)
Objectives

• Delineating the compounded effects of age and HIV-1 on the immune profile and disease prognosis is relevant for future therapeutics including potential immune reconstitution.

• Aim to assess impact of patient age on T-cell subset distribution, phenotype and functional memory responses to HIV-1, CMV and tetanus toxoid (TTox).
Methods

• Cross sectional analysis of 58 patients all receiving cART

• To assess relationship of patient age with
  
  ▪ T-cell Function:
    - IL-2, IFN-γ, Perforin, proliferation in response to
    - HIV-1 Gag peptides, CMV and TTox
  
  ▪ T-cell Phenotype:
    - differentiation (CD27/CD28; early, intermediate and late)
    - activation (HLA-DR/CD38)
    - co-stimulation/inhibition (CD28/CTLA-4)
    - senescence/exhaustion (CD57/PD-1)
Methods

• Multivariable model to identify significant independent predictors of T-cell phenotype and function incorporating:
  - Patient age
  - Time since HIV-1+ diagnosis
  - ART Duration
  - Nadir CD4 count
  - Current CD4 count
  - Current CD8 count
<table>
<thead>
<tr>
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<th>Age, years</th>
<th>Year of HIV-1+ diagnosis</th>
<th>Time since HIV-1+ diagnosis, years</th>
<th>ART duration, years</th>
<th>Nadir CD4+ T-cell count, cells/µl blood</th>
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Study Cohort (n=58)

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![Graphs showing correlations](image)
Patient Age

T-cell Function

**IL-2 response CMV**

\[ r^2 = 0.570 \]

\[ p = 0.049 \]

**IFN-γ response HIV-1 Gag\textsubscript{MHCI}**

\[ r^2 = 0.257 \]

\[ p = 0.038 \]

Patient age corrected for:
- Time since HIV-1\textsuperscript{+} diag.
- ART Duration
- Current CD4 count
- Nadir CD4 count
- Current CD8 count

Significant independent predictor with 95% confidence intervals

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T-cell Phenotype

**CD4 intermediate**

\[ r^2 = 0.436 \]

\[ p = 0.016 \]

**CD8 early**

\[ r^2 = 0.309 \]

\[ p = 0.010 \]

Patient age corrected for:
- Time since HIV-1\textsuperscript{+} diag.
- ART Duration
- Current CD4 count
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Significant independent predictor with 95% confidence intervals
ART Duration corrected for
- Patient Age
- Time since HIV-1\(^+\) diag.
- Current CD4 count
- Nadir CD4 count
- Current CD8 count

Significant independent predictor with 95% confidence intervals
Time Since HIV-1\textsuperscript{+} Diagnosis and Nadir

**T-cell Phenotype**

CD4 activated

\[
\begin{align*}
\% \text{CD3+CD4+} & \quad 100 \\
\text{CD3+HLA-DR+ events} & \quad 80 \\
0 & \quad 20 \\
5 & \quad 60 \\
10 & \quad 40 \\
15 & \quad 0 \\
20 & \quad 0 \\
25 & \quad 0
\end{align*}
\]

Time since HIV-1\textsuperscript{+} diagnosis, years

\[r^2 = 0.256, \quad p = 0.042\]

**Time HIV-1\textsuperscript{+} corrected for**

- Patient Age
- ART duration
- Nadir CD4 count
- Current CD4 count
- Current CD8 count

Significant independent predictor with 95% confidence intervals
Current CD4 and CD8 Counts

T-cell Phenotype

**CD8 early**

Current CD4 count, cells/µL blood

**CD4 activated**

Current CD4 count, cells/µL blood

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$\text{Current CD4 corrected for}$

| $r^2=0.309$ p = 0.007 |
| $r^2=0.250$ p = 0.007 |

Significant independent predictor with 95% confidence intervals
Summary

As patient **Age** increases it can be predicted that

- ↑ IFN-γ production to Gag$_{MHC}$, intermediate CD4
- ↓ IL-2 production to CMV, early CD8

Longer HIV-1 infection (**Time Since HIV-1$^+$ Diagnosis**) predicts an

- ↑ Activated CD4

Increased **ART Duration** is associated with

- ↑ Intermediate CD4
- ↓ Activated CD4, early CD4
Summary

Further support for early initiation of ART is demonstrated by

Nadir CD4

↑ Intermediate CD4
↓ Activated CD4

Current CD4

↑ Early CD4, early CD8
↓ Activated CD4

Current CD8

↑ Activated CD4
Although age is an important explanatory factor in immunological prognosis, T-cell function and phenotype, these data support early initiation and extended duration of cART (at a stage when CD4 counts are high, CD8 counts low, and time since HIV-1 diagnosis short) regardless of patient age.
Acknowledgements

Patients and Staff of the St Stephen’s Centre