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

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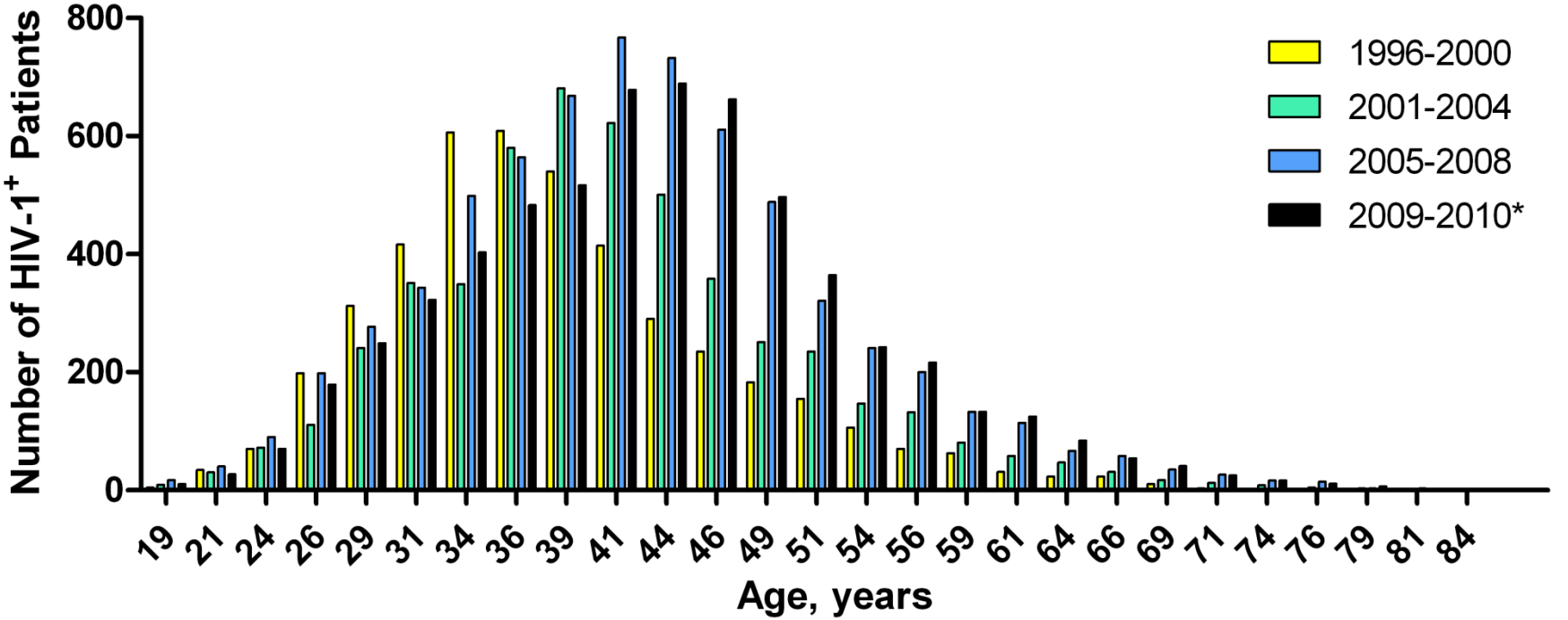
The Ageing Cohort (n=6106)



*Jan 2009-May 2010

- 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

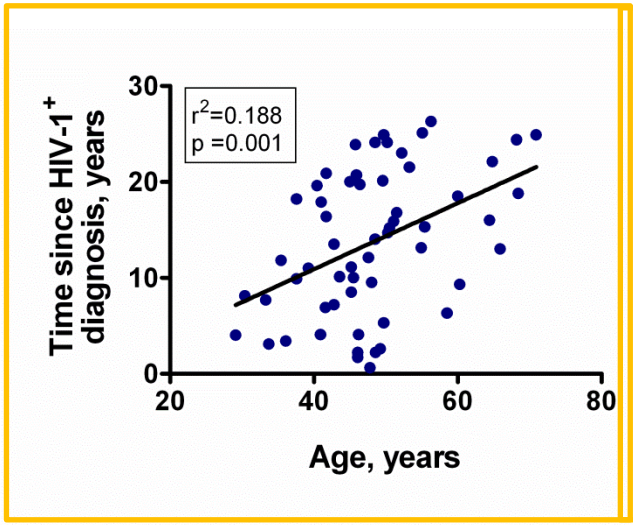
- Cross sectional analysis of 58 patients all receiving cART
- To assess relationship of **patient age** with
  - T-cell Function:
    - **IL-2**, **IFN-γ**, **Perforin, proliferation** in response to
    - **HIV-1 Gag** peptides, **CMV** and **TTox**
  - T-cell Phenotype:
    - **differentiation** (CD27/CD28; early, intermediate and late)
    - **activation** (HLA-DR/CD38)
    - **co-stimulation/inhibition** (CD28/CTLA-4)
    - **senescence/exhaustion** (CD57/PD-1)

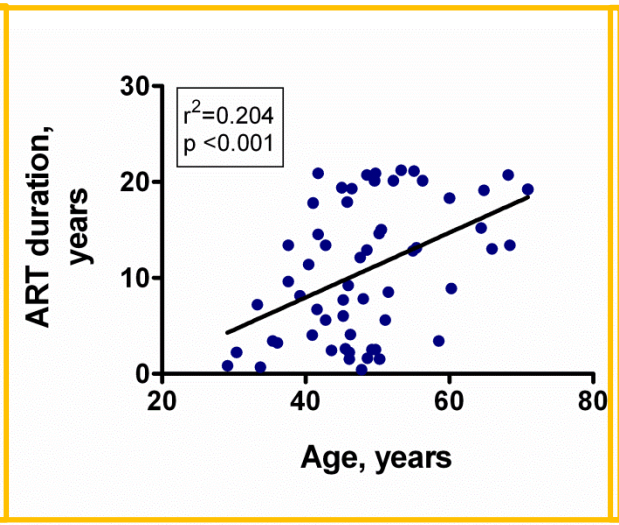
Methods

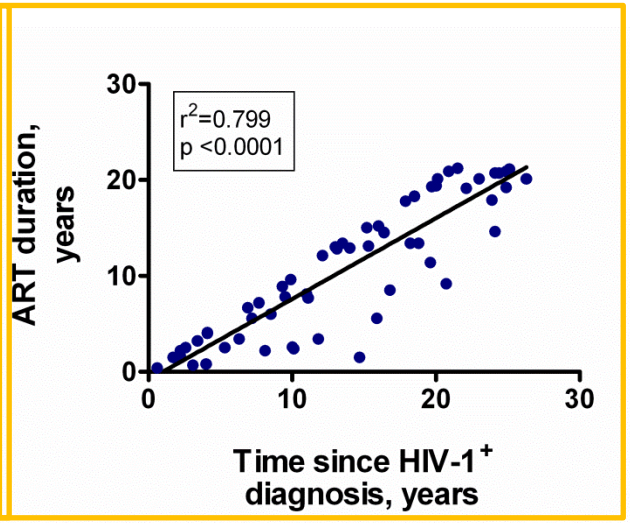
- Multivariable model to identify significant independent predictors of T-cell phenotype and function incorporating:
  - Patient age
  - Time since HIV-1^{+} diagnosis
  - ART Duration
  - Nadir CD4 count
  - Current CD4 count
  - Current CD8 count

Study Cohort (n=58)

	Age, years	Year of HIV-1$^+$ diagnosis	Time since HIV-1$^+$ diagnosis, years	ART duration, years	Nadir CD4+ T-cell count, cells/µl blood	CD4$^+$ T-cell count, cells/µl blood	CD8$^+$ T-cell count, cells/µl blood	Viral load, HIV-1 RNA copies/ml plasma
Median	47.7	1996	13.7	10.5	137	488	801	49
Range	*29.1 to 70.9*	*1984 to 2010*	*0.6 to 26.3*	*0.4 to 21.2*	*4 to 677*	*195 to 1426*	*271 to 1697*	*49*
IQR	*42.0 to 52.0*	*1990 to 2002*	*7.8 to 19.9*	*3.5 to 17.9*	*50 to 228*	*386 to 664*	*605 to 950*	*49*







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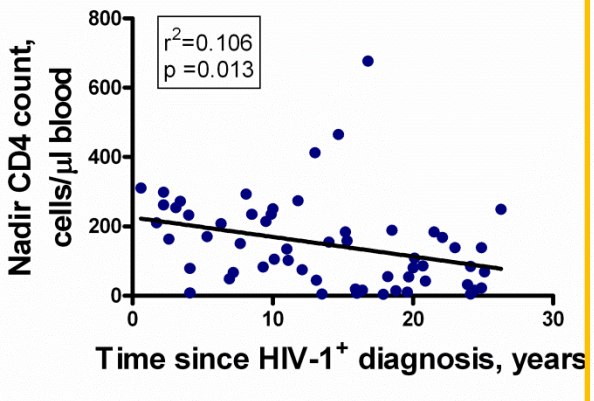
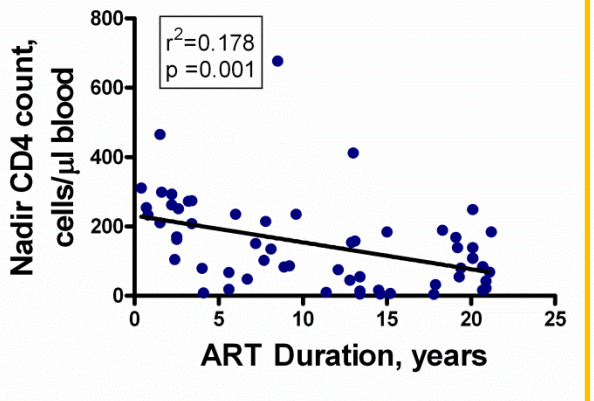
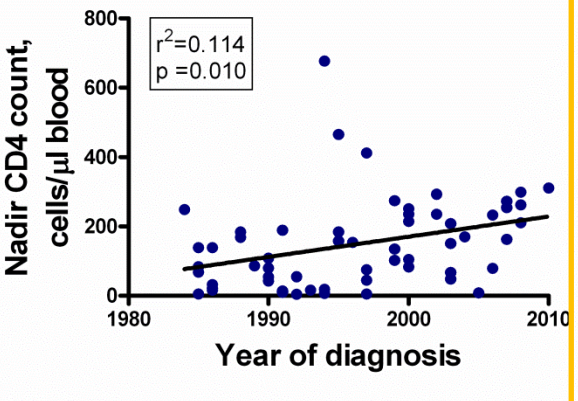


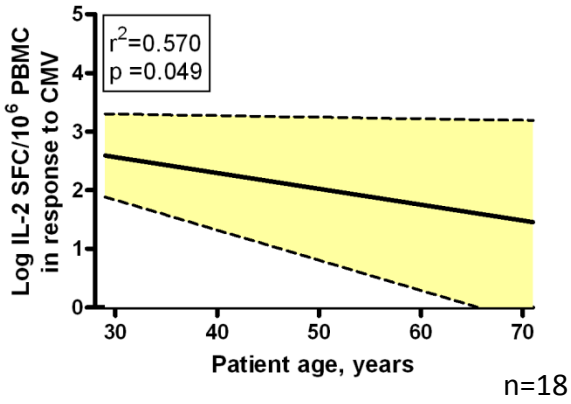




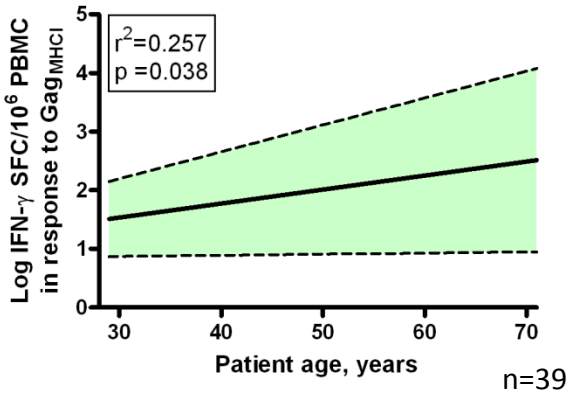
Patient Age

T-cell Function

IL-2 response CMV



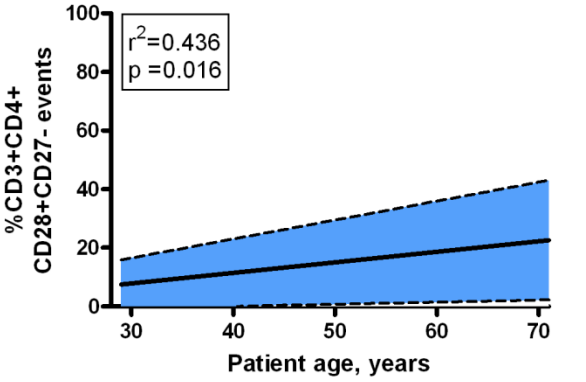
IFN-γ response HIV-1 Gag$_{MHCI}$



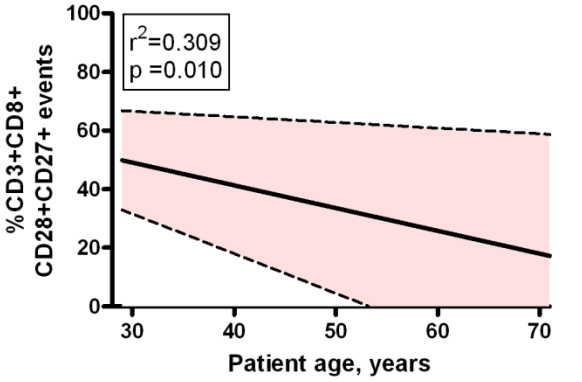
Patient age corrected for
- Time since HIV-1$^+$ diag.
- ART Duration
- Current CD4 count
- Nadir CD4 count
- Current CD8 count

T-cell Phenotype

CD4 intermediate



CD8 early

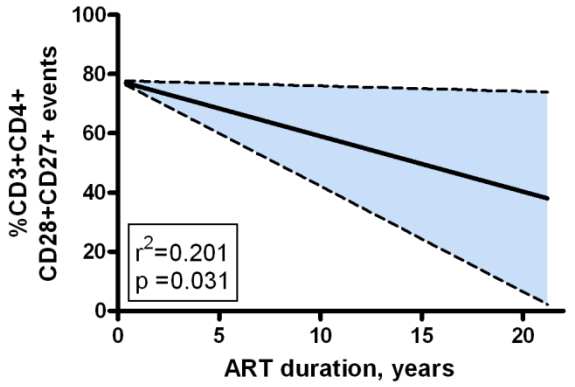


Significant independent predictor with 95%confidence intervals

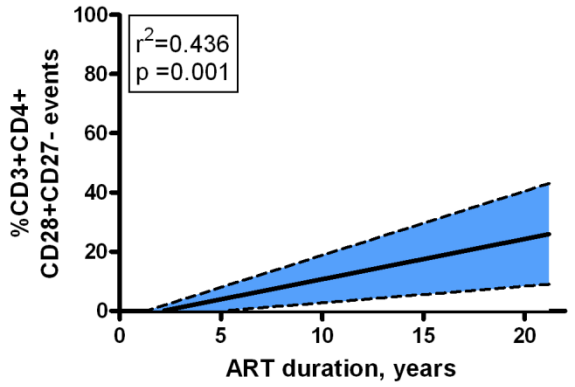
ART Duration

T-cell Phenotype

CD4 early



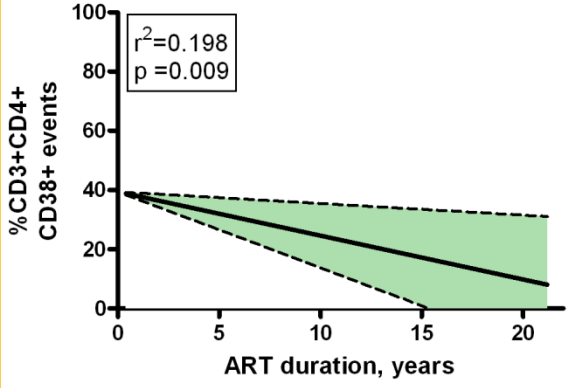
CD4 intermediate



ART Duration corrected for

- Patient Age
- Time since HIV-1$^+$ diag.
- Current CD4 count
- Nadir CD4 count
- Current CD8 count

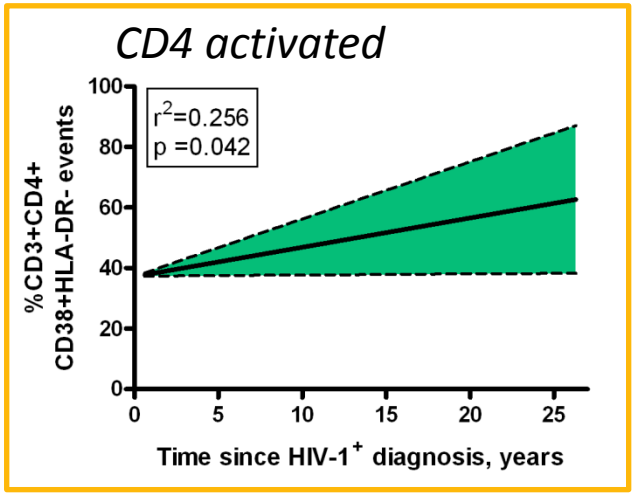
CD4 activated



Significant independent predictor with 95%confidence intervals

Time Since HIV-1$^+$ Diagnosis and Nadir

T-cell Phenotype



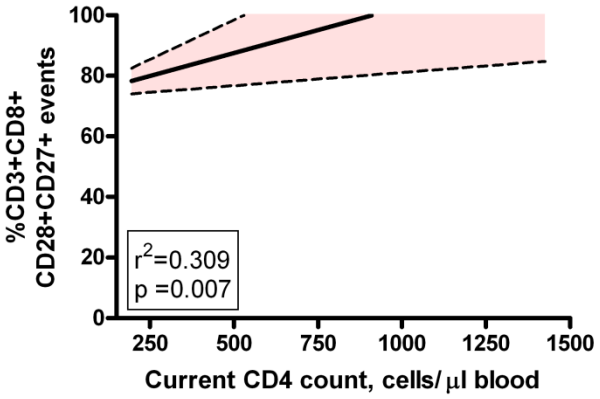
Time HIV-1$^+$ corrected for
- Patient Age
- ART duration
- Nadir CD4 count
- Current CD4 count
- Current CD8 count

Significant independent predictor with 95%confidence intervals

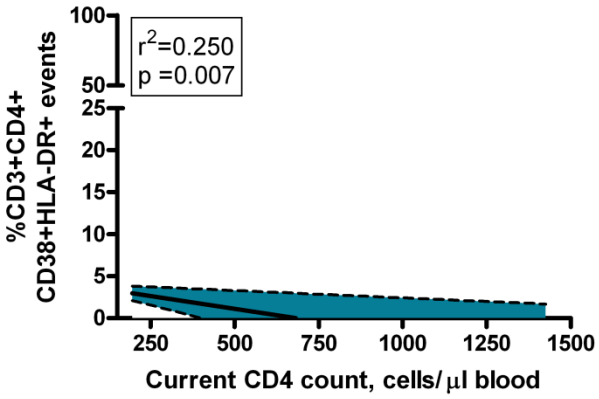
Current CD4 and CD8 Counts

T-cell Phenotype

CD8 early

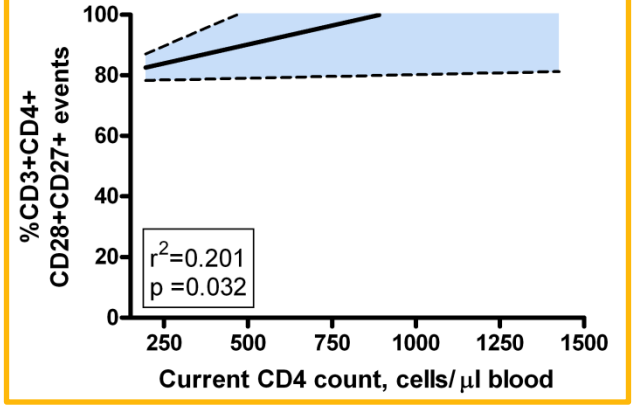


CD4 activated



Current CD4 corrected for
- Patient Age
- Time since HIV-1⁺ diag.
- ART duration
- Nadir CD4 count
- Current CD8 count

CD4 early



Significant independent predictor with 95%confidence intervals

Summary

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

↑ *IFN-γ production to* $Gag_{MHCI,}$ *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*

Conclusion

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

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Imperial College London

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