British HIV Association
BHIVA

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The antiviral inhibitory capacity of CD8+ T cells predicts the rate of CD4+ cell decline in HIV-1 infection

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Background
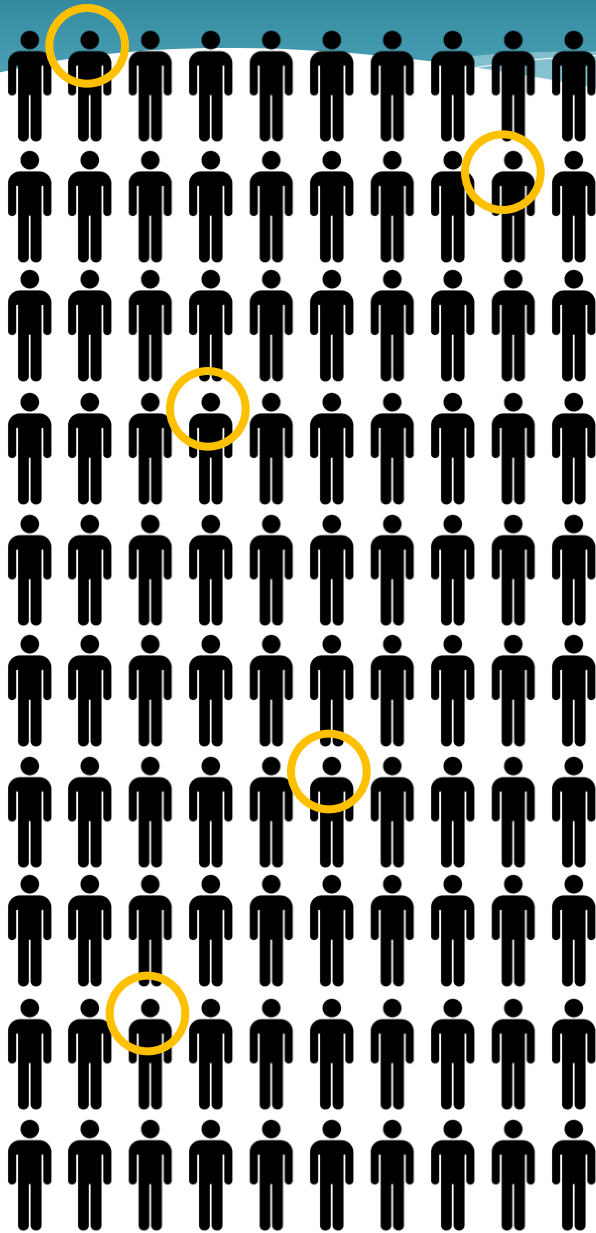
* HIV-specific CD8+ T cell responses control acute viraemia but fail to clear or control infection

* Superior functional capacity of HIV-specific CD8+ T cells from HIV controllers / long-term nonprogressors

* Cause or consequence of long-term virus control?

* Laboratory assays do not adequately reflect immune recognition of HIV in vivo

CD8+ T cell antiviral inhibitory activity: an immune correlate of HIV control?
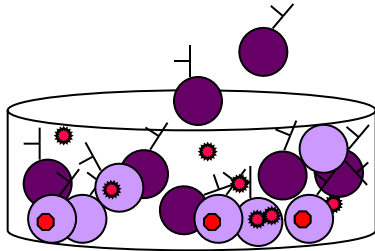
* Potent inhibition of HIV replication by ex vivo CD8+ T cells

  (Saez-Cirion et al., 2007, Freel et al., 2010)

* Unique to HIV controllers?

* A determinant of the rate of disease progression in viraemic individuals?

Aims

* To investigate the relationship between CD8+ T cell antiviral activity and HIV progression in chronic infection

* To determine whether CD8+ T cell antiviral activity in early HIV infection can predict HIV progression

Methods

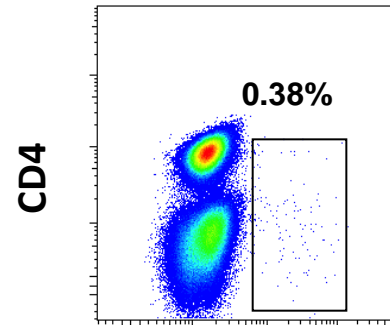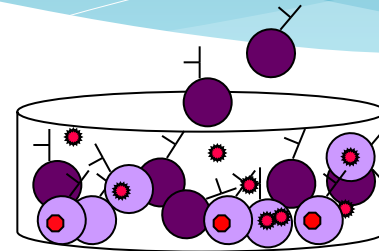Blood separated into CD4+ and CD8+ fractions

Activate CD4+ T cells then super-infected with HIV

Autologous unstimulated CD8+ T cells added on day 3

5.1%

CD4
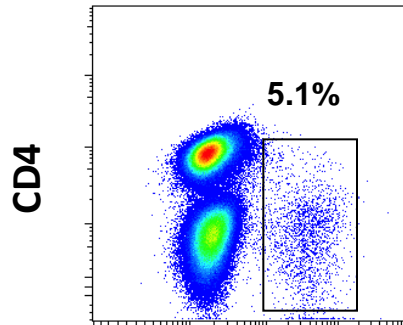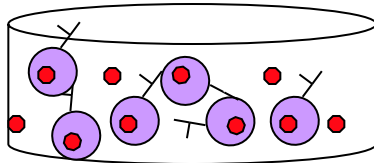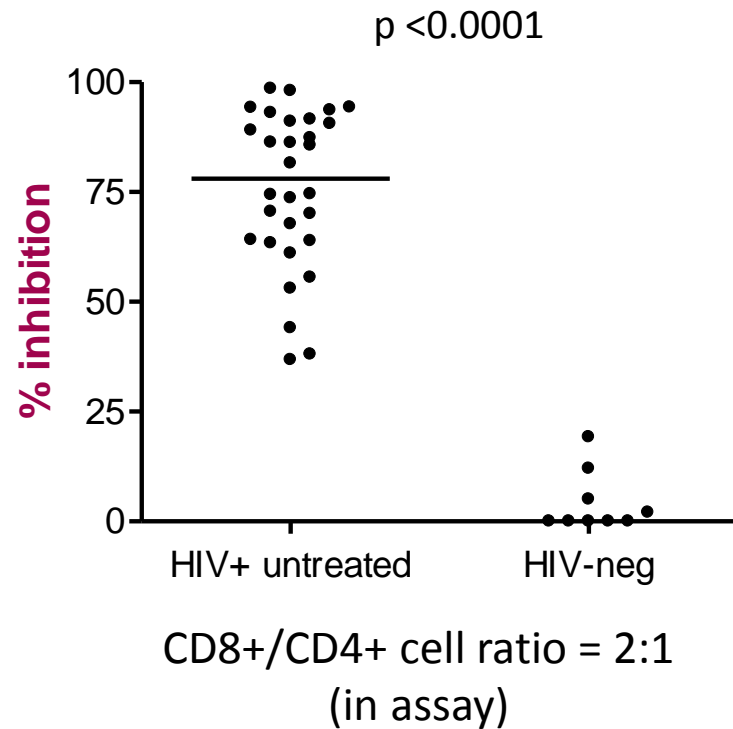
HIV p24 antigen

Culture for 5-7 days

0.38%

CD4

HIV p24 antigen

Reduction in viral growth by CD8+ T cell is expressed as **% inhibition**

$$\frac{\text{(\% infected CD4+ cells (p24}^{+)} \text{ in CD4/CD8 co-culture)}}{\text{\% infected cells in CD4+ cells alone}}$$

# CD8+ T cell antiviral activity is expressed on a continuum in chronic HIV infection

* 30 patients with chronic HIV infection, ART-naïve, asymptomatic
* CD4 counts > 350 cells/µl
* 20 males, 10 females
* Median age - 34 yrs
* Median diagnosed infection: 3 years

* Protective HLA class I allele - 20%

p <0.0001

% inhibition

100

75

50

25

0

HIV+ untreated   HIV-neg

CD8+/CD4+ cell ratio = 2:1
(in assay)

CD8+ T cell antiviral suppressive activity in chronic HIV infection is strongly associated with the rate of CD4+ cell decline

CD4 slopes derived from median 4.5 years' follow-up

Linear mixed models to investigate interaction between CD4 slope and CD8+ T cell antiviral activity (% inhibition)
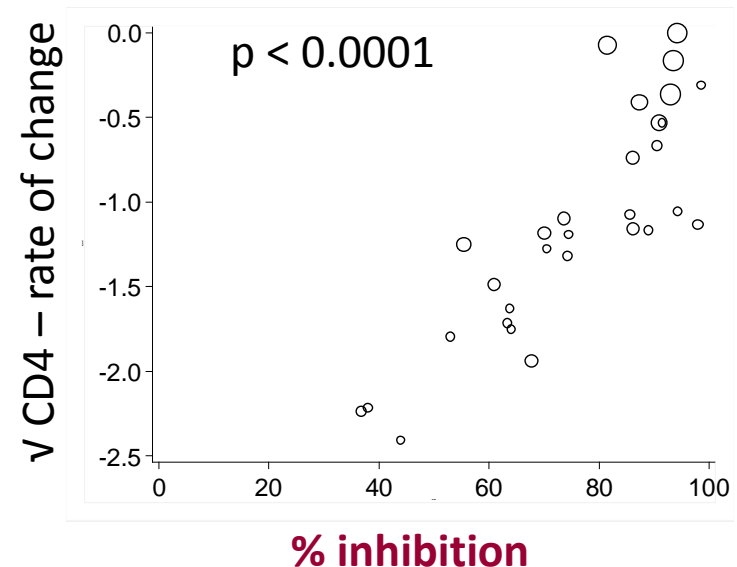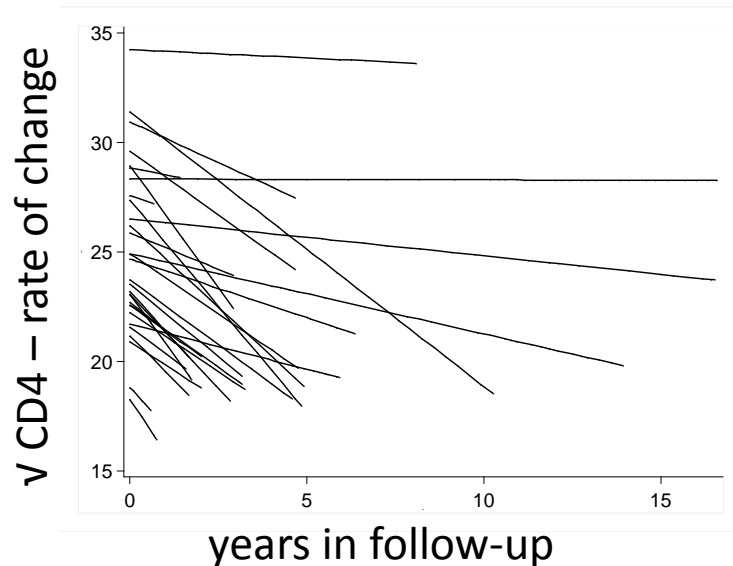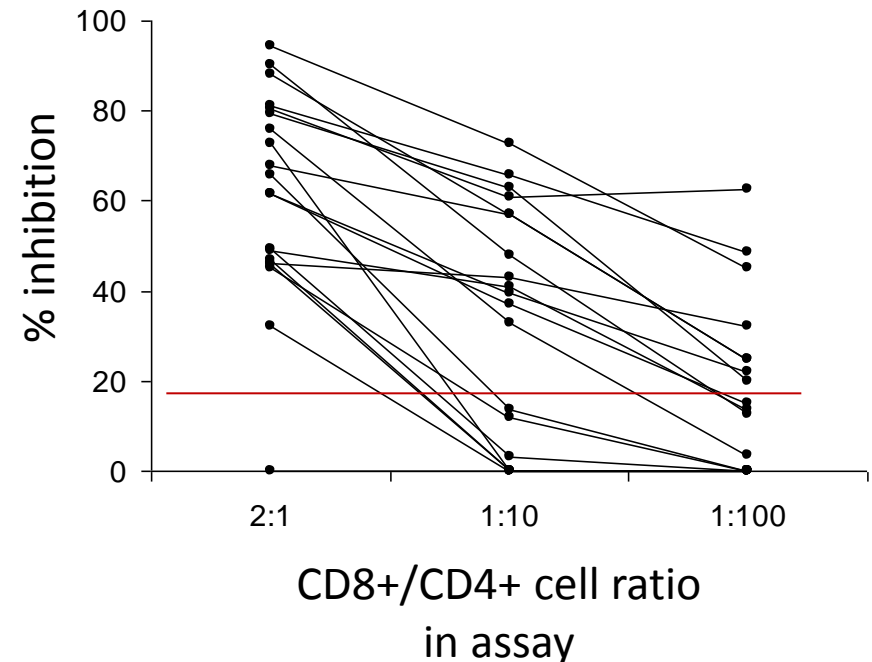
Is potent CD8+ T cell antiviral activity the cause or consequence of HIV disease control?

- Prospective study in recently infected patients with known date of HIV-1 acquisition – Beijing PRIMO cohort

- CD8+ T cell antiviral activity measured at a single time-point in early infection

- Examined predictive value of % inhibition for the rate of CD4 decline over first 3 years of infection

# Prospective analysis of 20 patients with recent HIV infection

* 20 MSM, ART-naïve, asymptomatic
* CD4 counts > 350 cells/µl
* Median age - 28 yrs

* CD8+ T cell antiviral activity measured at single time-point at 3 CD8+/CD4+ cell ratios
* Duration of infection: median 198 days
* Follow-up: median 895 days

* Protective HLA class I allele*: n = 6 (30%)

Linear mixed models analysis

* CD8+ T cell antiviral activity was a strong predictor of the rate of CD4+ cell decline at all CD8+/CD4+ cell ratios tested (p < 0.0001)

* Explained up to 73% of inter-individual variation in CD4 slope

Potent CD8+ T cell antiviral activity is associated with longer survival with CD4 > 350 cells/µl

p = 0.06

CD8/CD4 = 2:1

% subjects with CD4 count >350

p = 0.0002

CD8/CD4 = 1:10
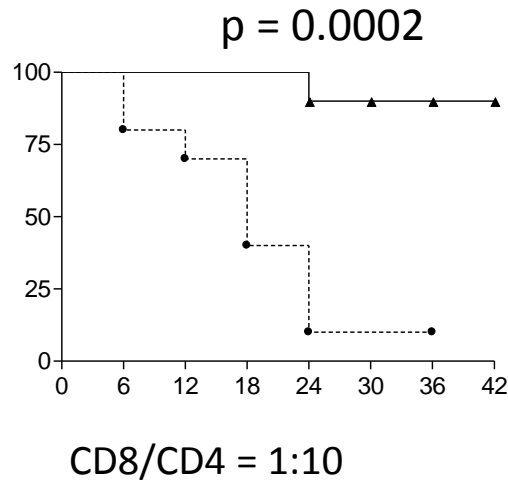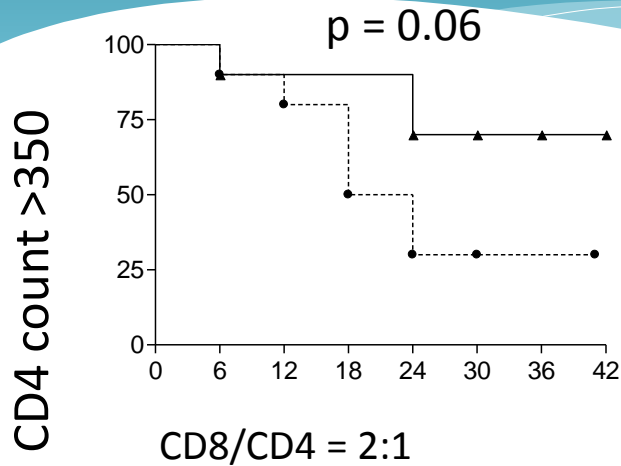
Patients stratified by % inhibition value above ▲ or below ◆ median

p = 0.003

CD8/CD4 = 1:100

months since infection
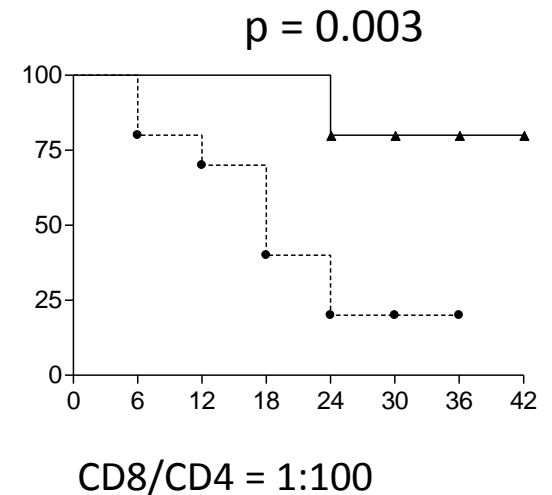
Summary

* Assay enables measurement of 'total' HIV-specific CD8+ T cell response

* The capacity of CD8+ T cells to inhibit HIV replication in vitro is:

  - highly predictive of the rate of CD4+ cell decline in the first 3 years of infection

  - explains majority of inter-individual variation in CD4 slope

  - inversely correlated with viral load set-point

Implications

* Assessment of CD8+ T cell function could have prognostic value in patients with CD4 counts above current thresholds for ART-initiation

* Potential as a benchmark of effective immunity in the clinical evaluation of HIV vaccine candidates

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