The role of viral fitness in HIV-1 disease progression

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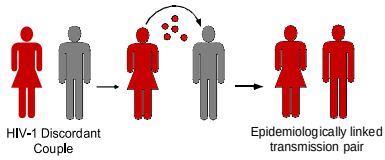
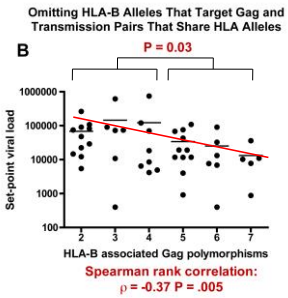
Follow-up after HIV-1 transmission in discordant couples



Follow-up newly infected partner for up to 8 years with longitudinal CD4 and viral load (VL).
Allows us to analyze the impact of immune selection in the donor on virus replication and disease progression in the recipient over more than 5 years

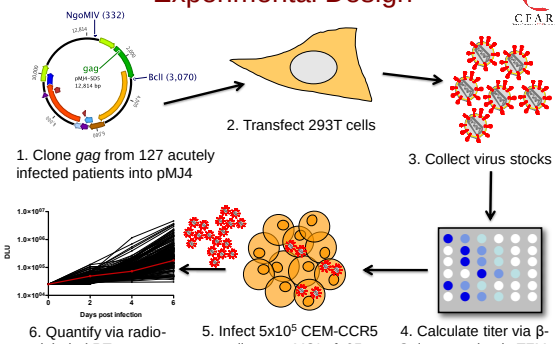
The more CTL escape mutations in Gag results in lower set-point viral loads in newly infected linked recipients.



Extension of analysis of Goepfert et. al. *J Exp Med.* 2008

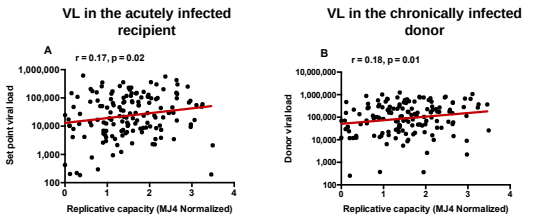
To what degree does the viral replicative capacity, defined by the *gag* gene, of the transmitted virus contribute to the set-point viral load and early pathogenesis of a newly infected individual?

Experimental Design



Prince, Claiborne et al. PLoS Pathogens 2012

Viral replicative capacity is a heritable component affecting viral load

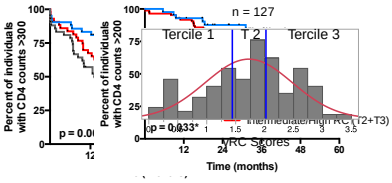


vRC is positively correlated with plasma VL in 149 linked transmission pairs

How does vRC affect pathogenesis in terms of CD4+ T cell decline?

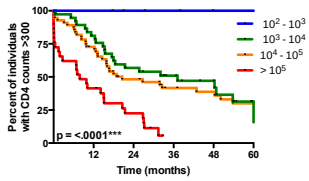
Prince J, Claiborne D et al., *Plos Path*, 2012

vRC of the transmitted Gag sequence influences CD4+ T cell decline



What is the mechanism?

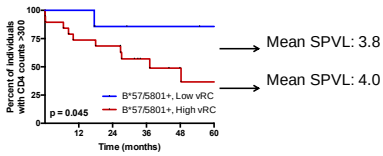
Set point VL is an established predictor of CD4+ T cell decline



We know that vRC is associated (albeit weakly) with early set-point VL.
Could the impact of vRC on CD4 decline just be a result of the higher VL associated with high vRC

vRC is independent of, but additive with, the effect of Set point VL and protective HLA alleles

B*57/5801 Positive Individuals

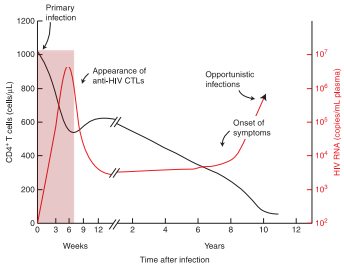


Cox Proportional Hazards Model (Time to CD4<300)

Factors Tested	HR	95% CI	*P*-value
Female	1.10	.67–1.70	.78
Low vRC (lowest tercile)	.48	.28–.80	0.004
B*57/5801	0.45	.23–.81	.006
Set point VL	10.00	2.86–44.14	.0004

If vRC affects CD4+ T cell decline independently of viral control,
we hypothesize vRC is influencing the early inflammatory environment.

Early viral replication before host responses: Irreversible damage with no turning back?



We hypothesized that infection with high vRC viruses could:

- Influence the early inflammatory cytokine response and microbial translocation
- Result in increased activation, exhaustion, and proliferation of key T-cell populations
- Give rise to elevated infection and/or depletion of key memory CD4+ T cell subsets

Experimental Approach

1. Measure levels of inflammatory cytokines and markers of microbial translocation in plasma at 0 (seroconversion, 45 days post EDI) months post-infection.

1. Determine levels of cellular immune activation and exhaustion, specifically in the T cell compartment.

1. Evaluate viral burden and cellular depletion of different memory CD4 T cell compartments.

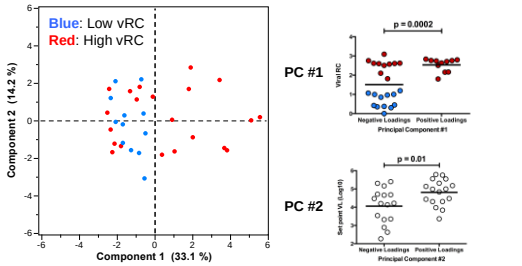
High vRC is associated with increased levels of pro-inflammatory cytokines early in infection

Analyte	Low vRC (mean pg/mL)	High vRC (mean pg/mL)	p-value
IL-10	5.5	10.73	0.004
IL-6	1.88	3.94	0.004
IL-1β	0.21	0.57	0.008
IFNγ	4.38	10.26	0.014
IP-10	639.56	1108.43	0.018
TNFα	10.76	13.87	0.028
IL-7	1.81	2.65	0.046
IFNα2	21.09	31.48	0.048

- High RC is significantly associated with an increase in inflammatory cytokine levels at an early time point post infection (45 days)
- The expression levels of many of these inflammatory mediators are highly correlated – we have therefore employed Principal Component analysis to define “inflammatory profiles” associated with different variables

Eileen Scully and Marcus Altfeld, Ragon Institute

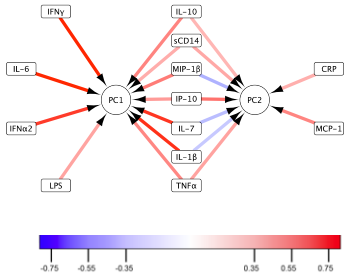
Principal component analysis (PCA) of cytokines at seroconversion



PC#1 and PC#2 describe distinct cytokine profiles associated with vRC and set point VL, respectively

Eileen Scully and Marcus Altfeld, Ragon Institute

Principal Component Analysis (PCA) defines distinct inflammatory profiles



Experimental Approach

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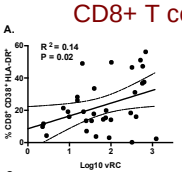
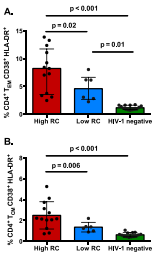
vRC is associated with aberrant CD8+ T cell phenotypes



High vRC associated with increased activation and reduced cytotoxic potential

Gladys Macharia, Jakub Kopycinski, Jill Gilmour, **IAVI**

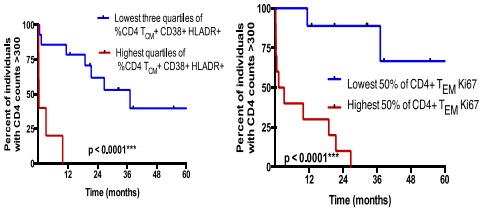
vRC is associated with aberrant CD4+ T cell phenotypes



- High vRC is associated with increased activation and proliferation of memory CD4s
- Individuals with low RC viruses, in general, have CD4+ T cell phenotypes more closely resembling that of uninfected individuals

Gladys Macharia, Jakub Kopycinski, Jill Gilmour,

The aberrant CD4+ T cell phenotypes are associated with rapid CD4 decline



- These activation and proliferation phenotypes are highly deleterious

Gladys Macharia, Jakub Kopycinski, Jill Gilmour,

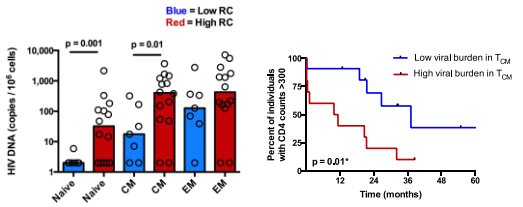
Experimental Approach

1. Measure levels of inflammatory cytokines and markers of microbial translocation in plasma at 0 (seroconversion, 45 days post EDI), 3 and 6 months post-infection.

1. Determine levels of cellular immune activation and exhaustion, specifically in the T cell compartment.

1. Evaluate viral burden and cellular depletion of different memory CD4 T cell compartments.

vRC affects viral burden in CD4+ T cell subsets



- vRC drives infection of naïve and CM CD4+ T cells
- This suggests that individuals infected with low RC viruses may have smaller viral reservoirs, and might be better candidates for cure strategies

Conclusions from current study

- We show that infection by high vRC virus is:
  - linked to an inflammatory state early in infection that is characterized by elevated levels of key inflammatory cytokines known to drive pathogenesis.
  - associated with aberrant CD8 and CD4 T cell phenotypes characterized by increased levels of cellular activation, exhaustion, and proliferation.
  - Characterized by increased viral burden in naïve CD4+ T cells and CD4+ Tcm cells.

Thus the nature of the virus initiating infection has a dramatic impact on immune control of virus and disease progression.

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