Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
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HIV acute infections and elite controllers- what can we learn?

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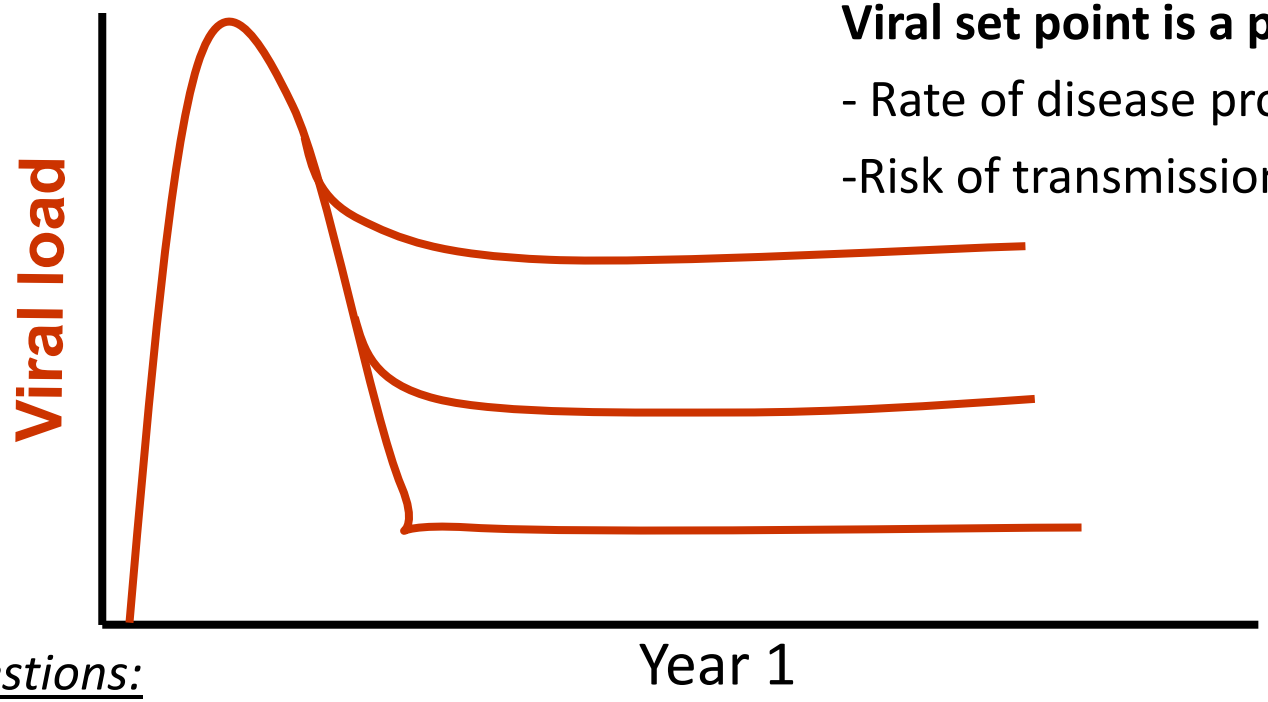
SOUTHERN AFRICAN HIV CLINICIANS SOCIETY 2016

Outline

- Acute HIV infection- public health importance and challenges of research
- Some lessons on HIV immunopathogenesis from acute infection studies (host restriction factors and CD8+ T cells)
- Elite and viremic controllers
- Lessons from viremic and elite controllers on viral control mechanisms

Acute HIV-1 infection- what lessons can we learn?



Viral set point is a predictor for:

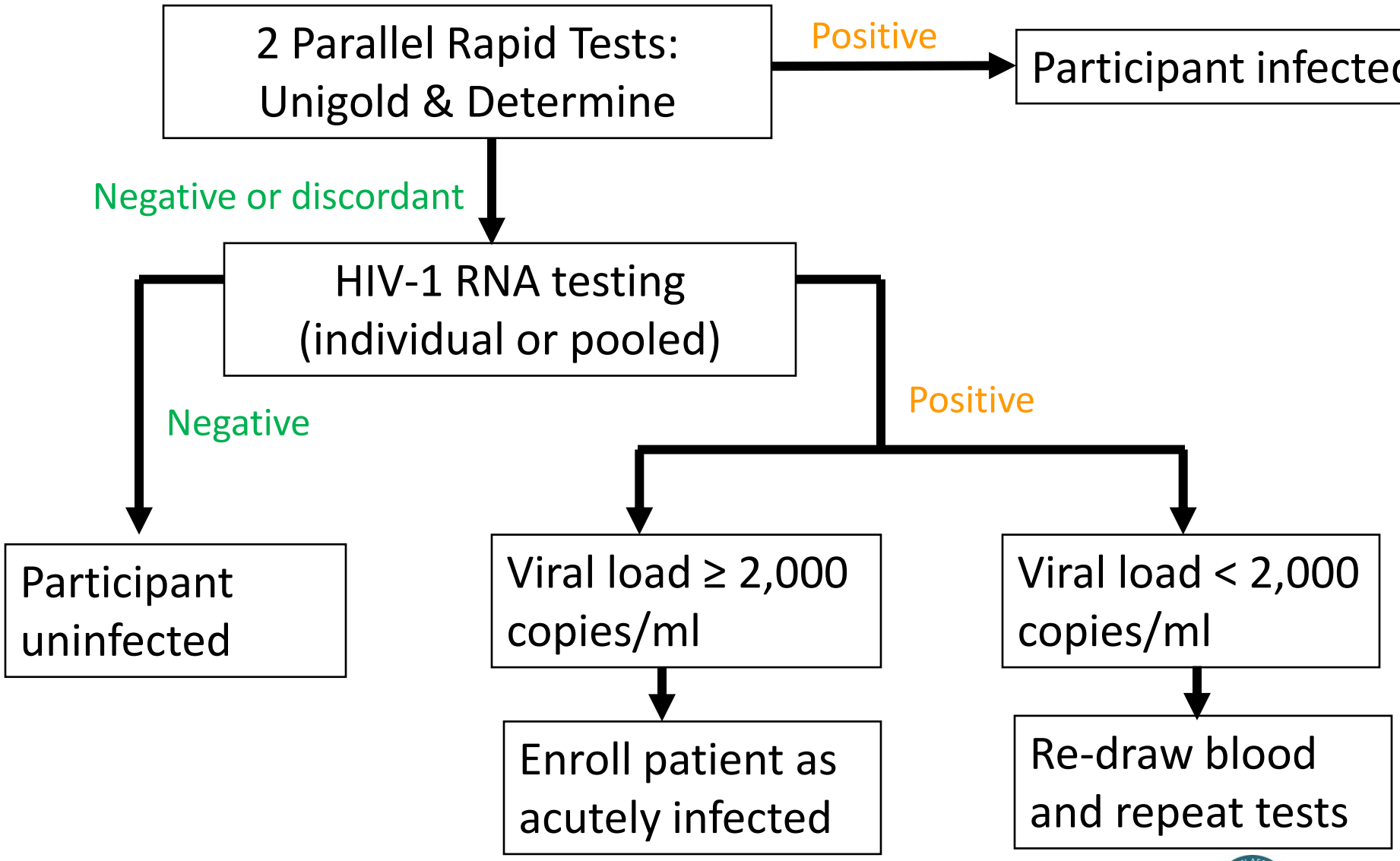
- Rate of disease progression

-Risk of transmission

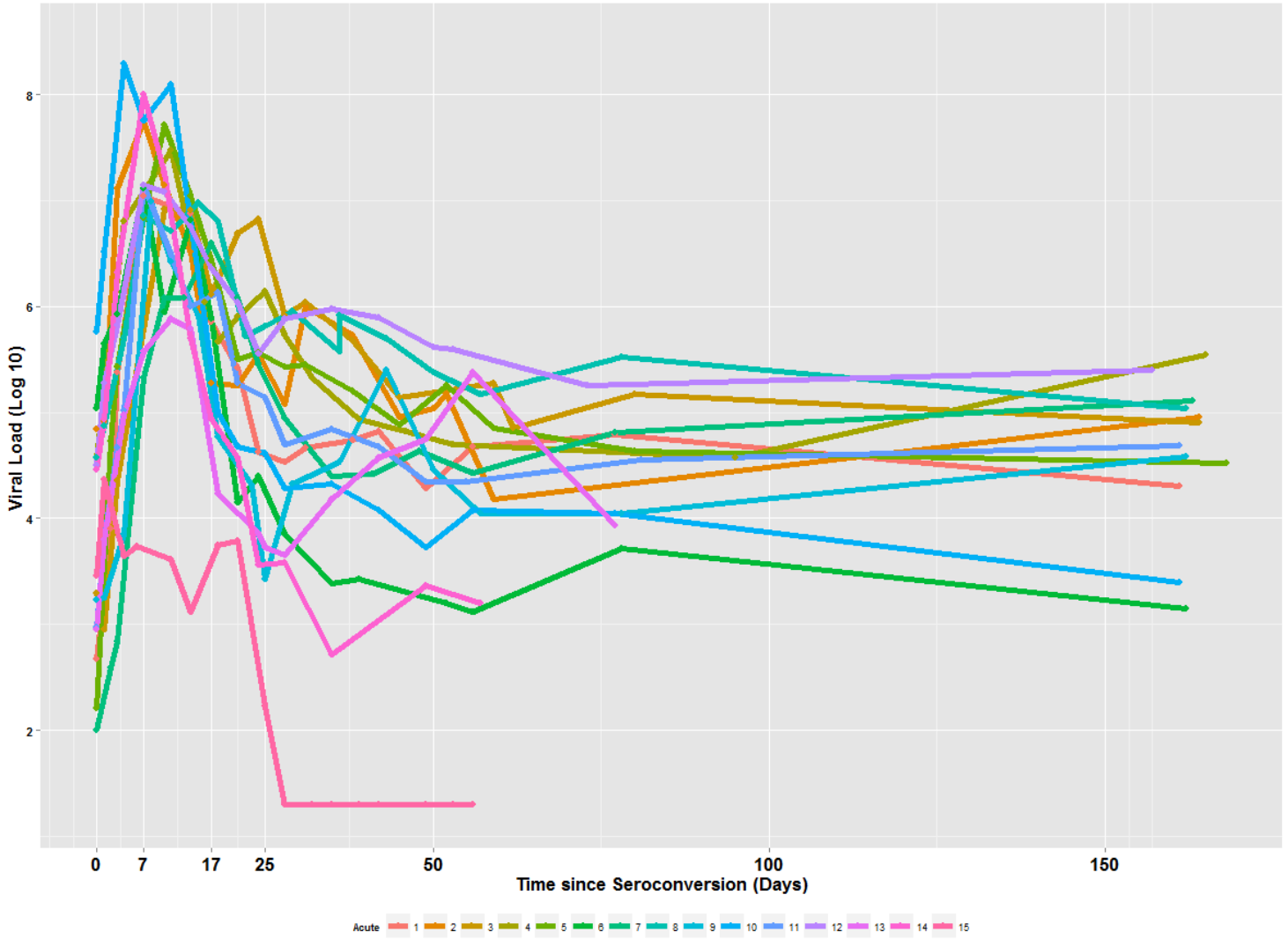
Key questions:

- What behavioural, socioeconomic and biomedical factors are responsible for continuing high incidence especially among young women?
- What is the nature of the transmitted/founder virus?
- What do immune responses in acute HIV-1 infection look like and why do they ultimately fail in most cases?

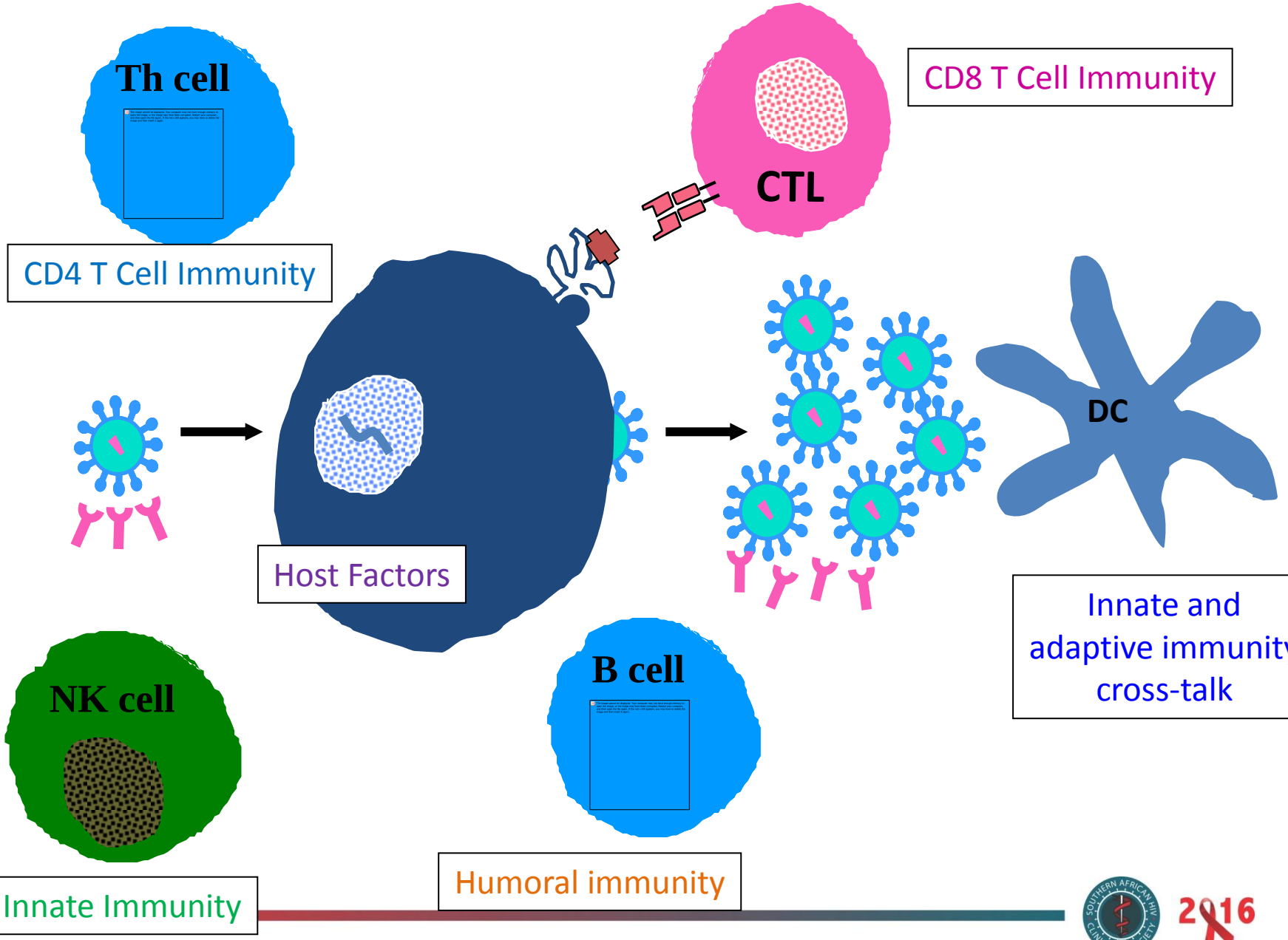
Individual or pooled plasma acute infection testing algorithm



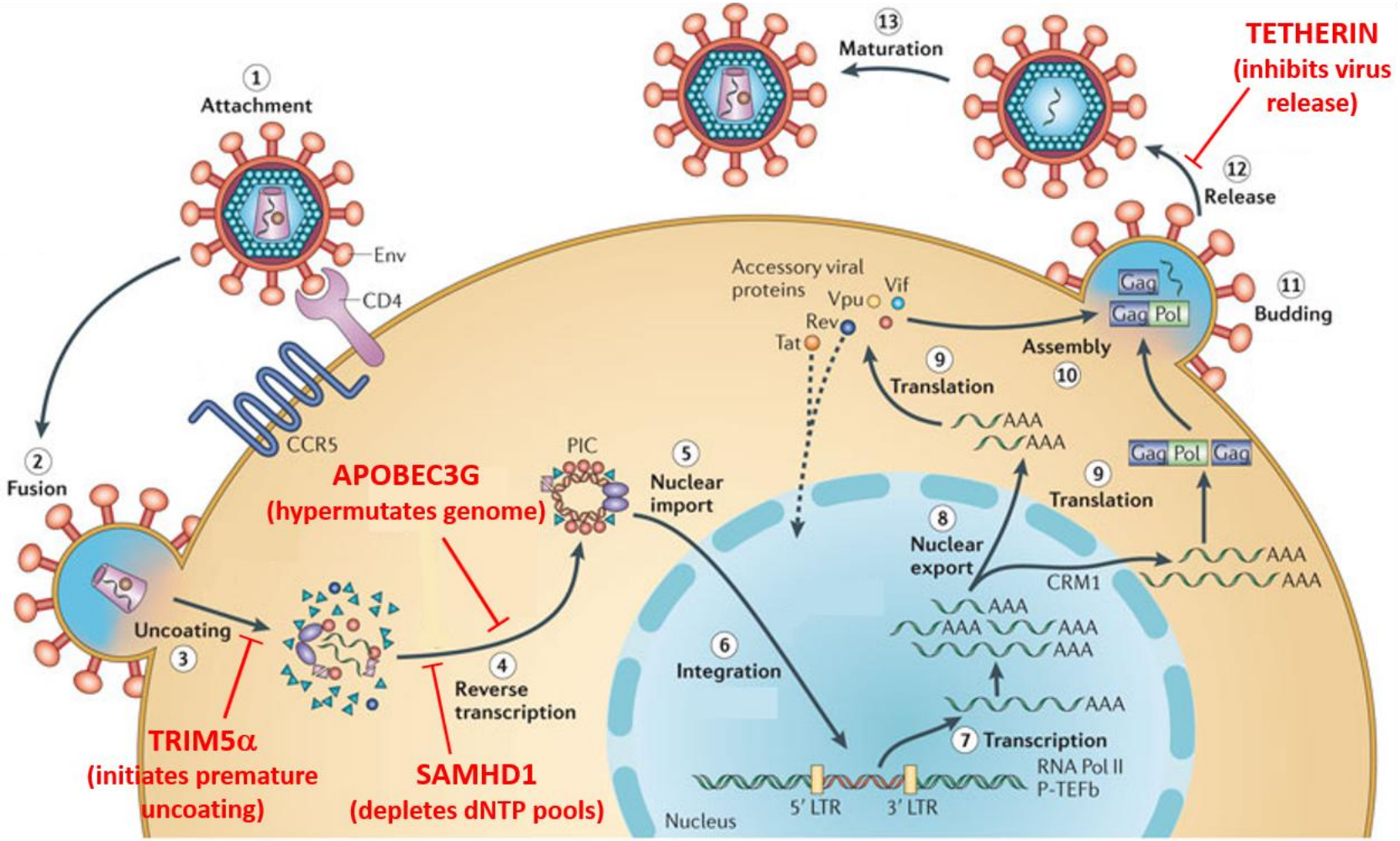
Acute HIV infection viral load trajectory and set point



Simple schema of the immune system

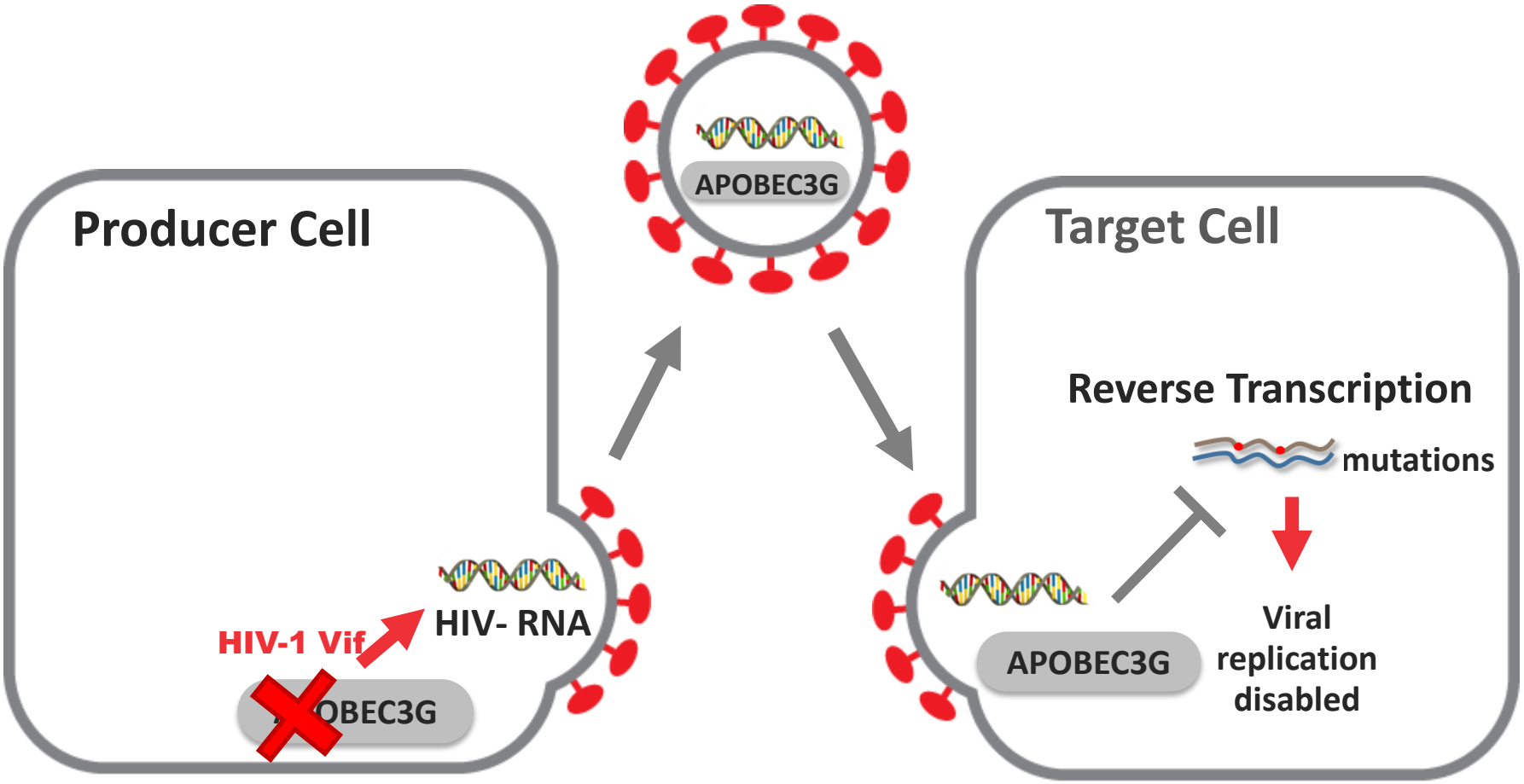


Sites of Host Restriction Activity in HIV Life Cycle

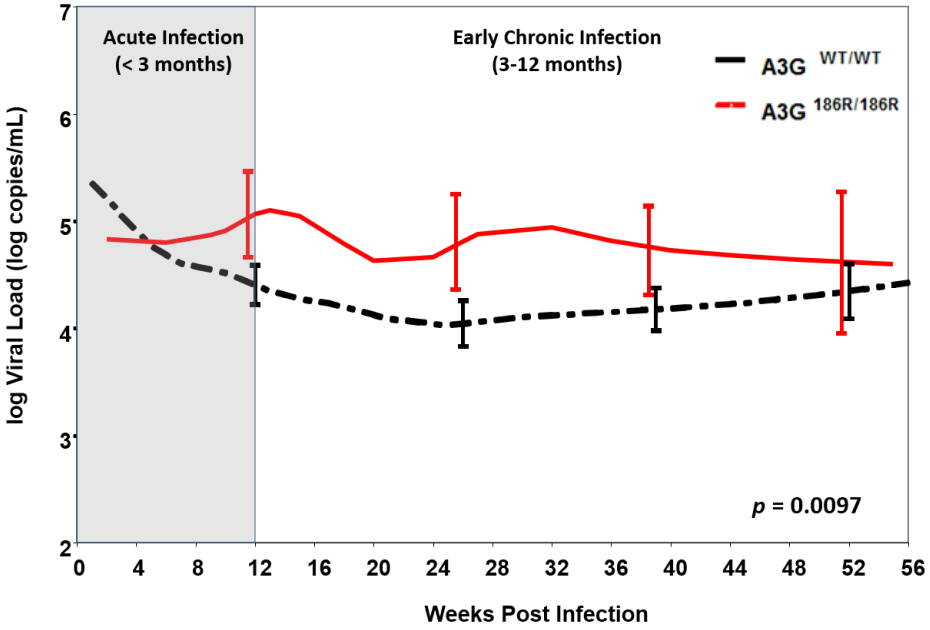


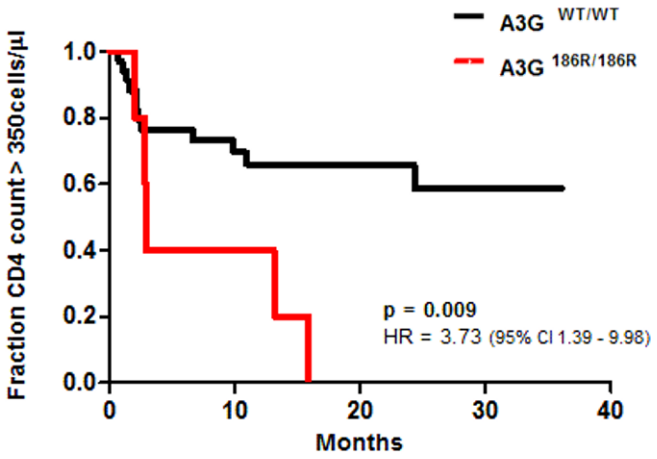
Engelman and Cherepanov, *Nature Reviews Microbiology*, 2012

APOBEC3G: an intrinsic block to HIV



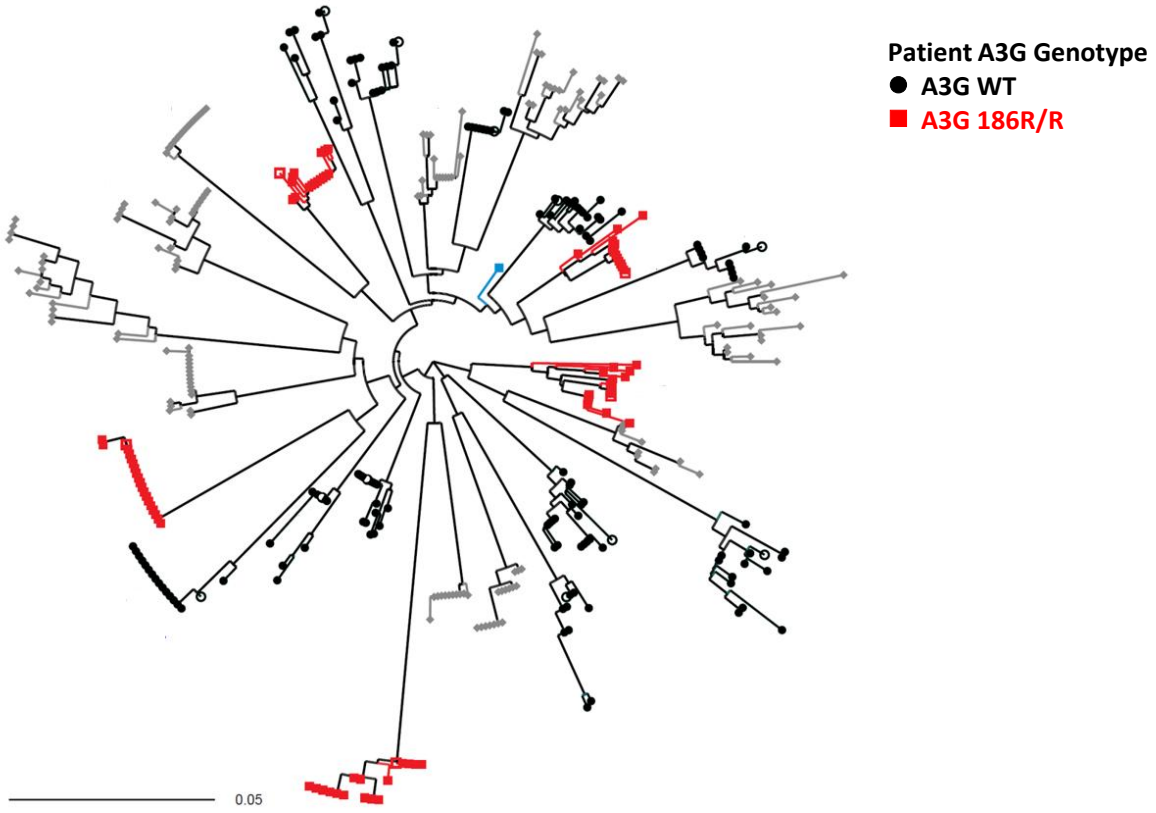
APOBEC3G H186R is associated with high viral load and rapid CD4 decline





Reddy et. al., 2010, *AIDS*

Patient derived Vif clonal sequences cluster independently of APOBEC3G H186R genotype



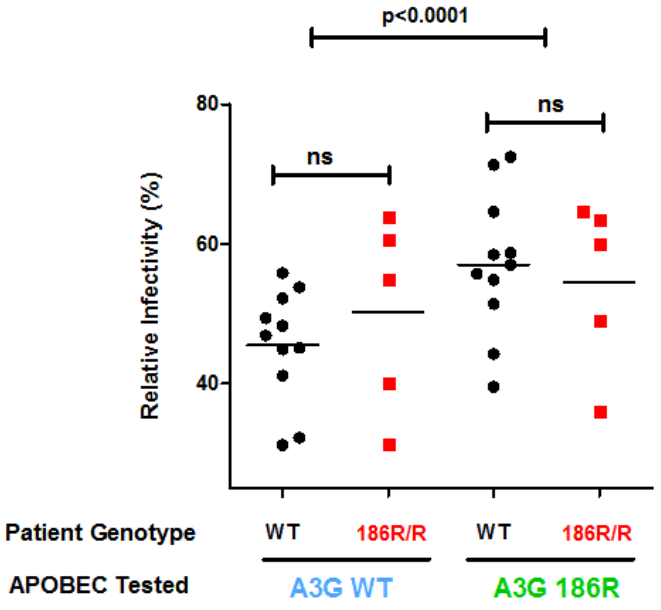
APOBEC3G variants: hypothesis and aims

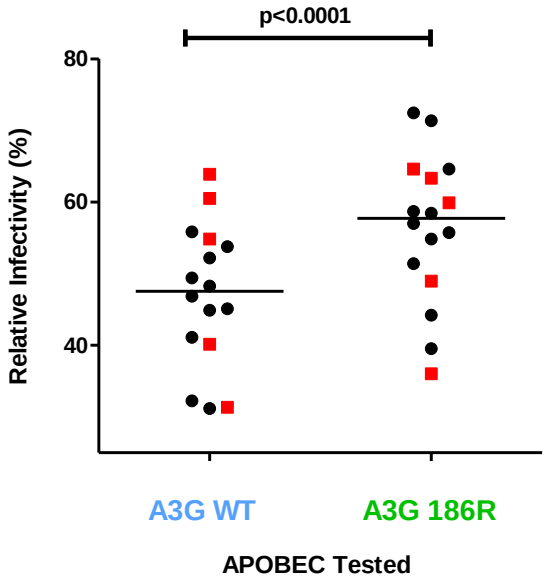
Hypothesis: The Vif protein adapts to APOBEC3G immune pressure according to APOBEC3G haplotypes with differential ability to inhibit HIV replication

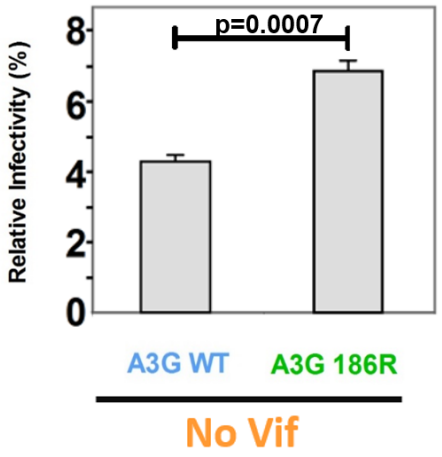
Specific Aims:

1. Assessment of Vif genetic diversity according to genotypes with different infection outcomes
2. Functionally characterize Vif variants from patients with different APOBEC3G genotypes and their ability to degrade APOBEC3G variants

Vif activity is independent of patient A3G genotype and A3G WT restricts HIV more efficiently than 186R







Vif derived from patient A3G
- A3G WT
- A3G 186R/R

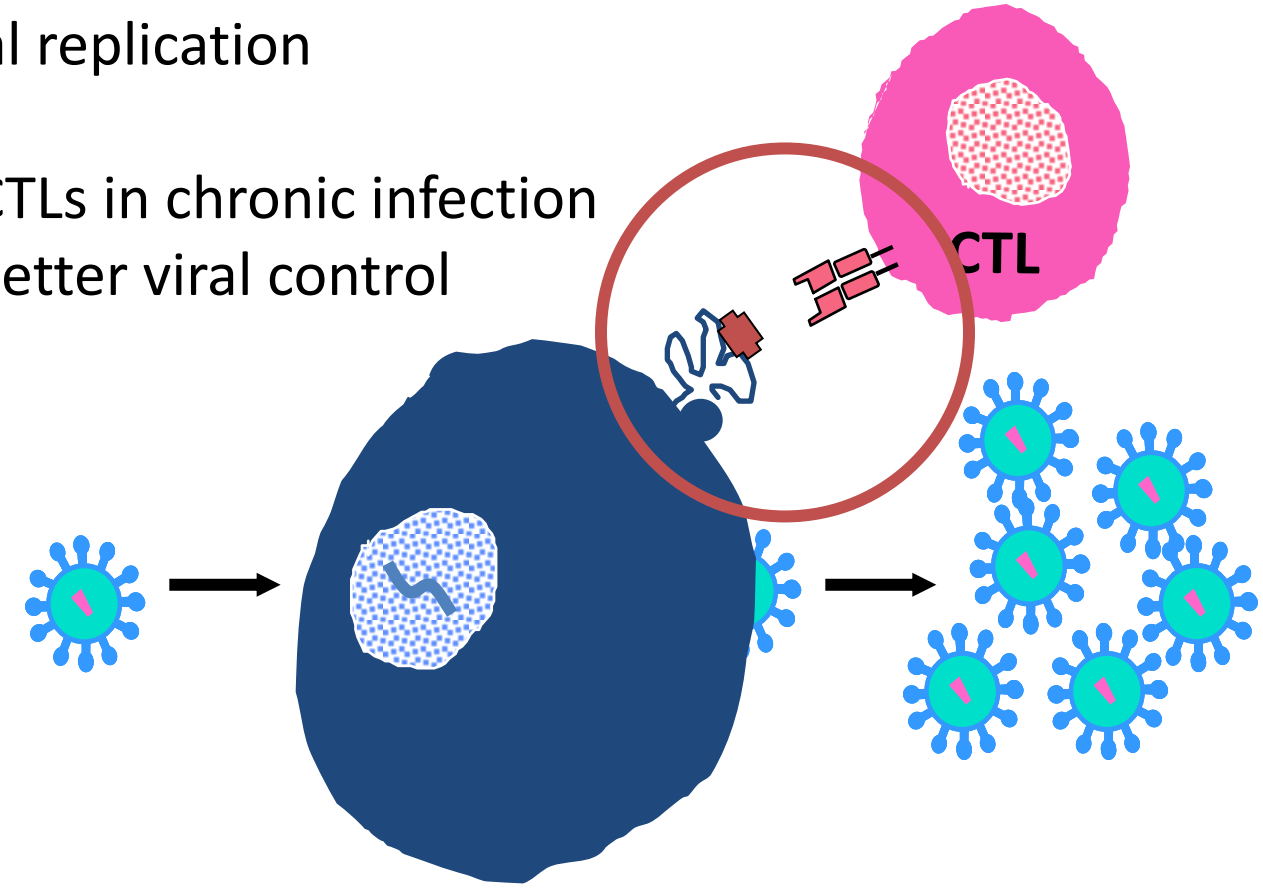
Conclusions I

- A3G WT and A3G-H186R are equally susceptible to counteraction by Vif.
- A3G-H186R variant intrinsically displayed lower antiviral activity.
- We speculate that A3G-H186R may have:
  - reduced deaminase activity.
  - inefficient packaging into virions.
- Understanding sites of host/virus interaction can be targeted by novel therapy approaches for the treatment of HIV.

Evidence for role of CTLs in HIV control

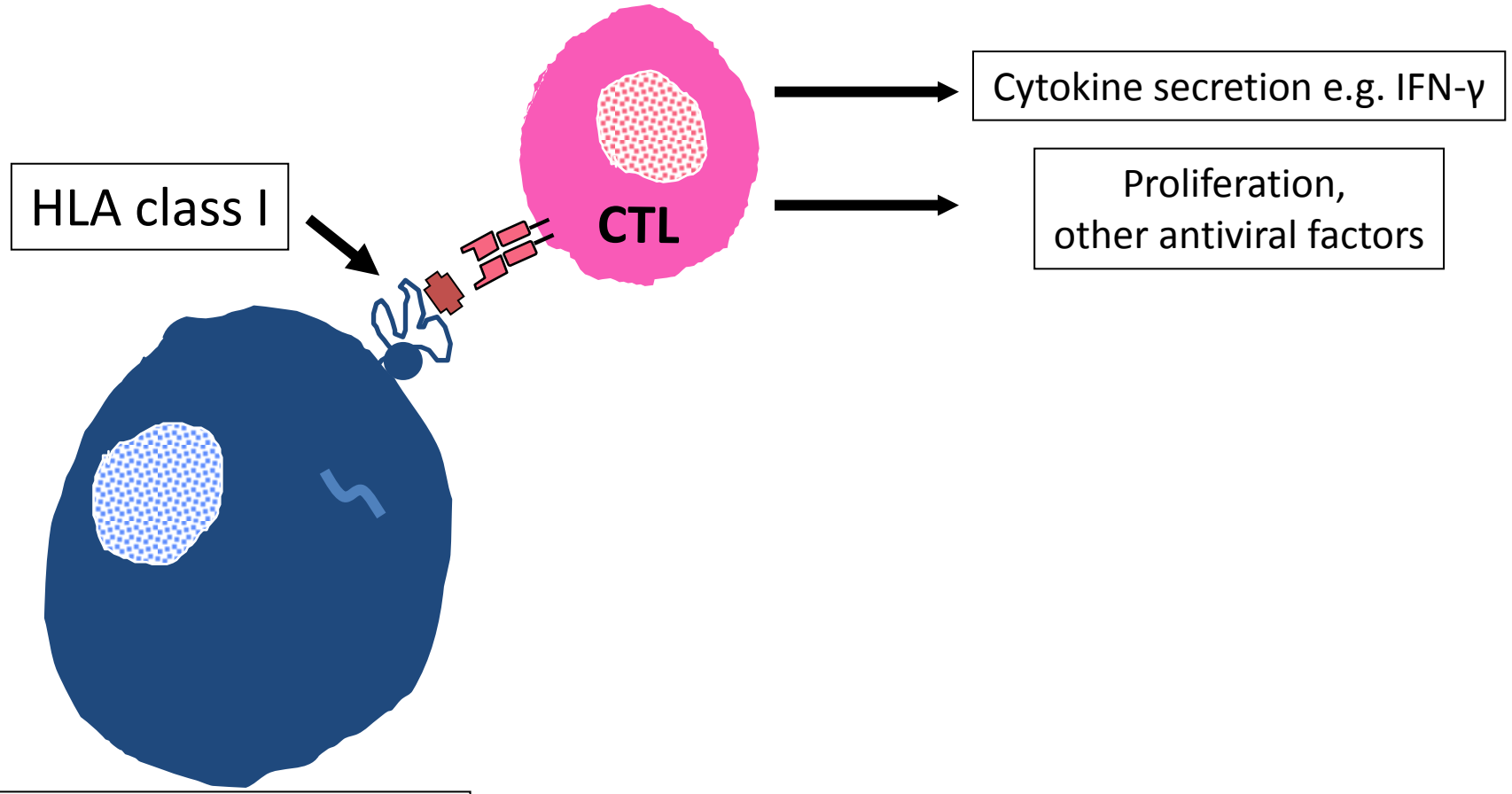
- In animal models, depletion of CTLs results in uncontrolled viral replication

- Breadth of Gag CTLs in chronic infection correlates with better viral control

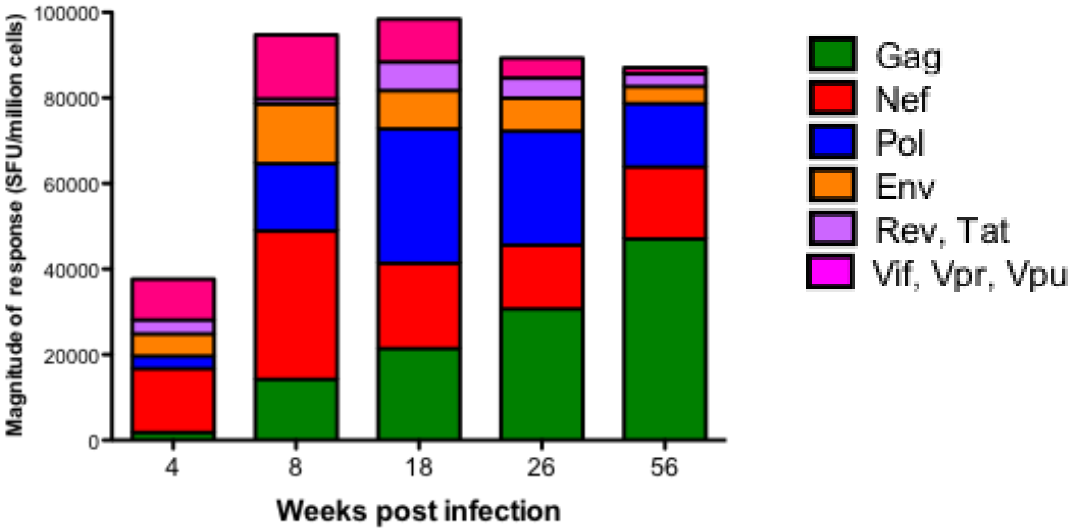


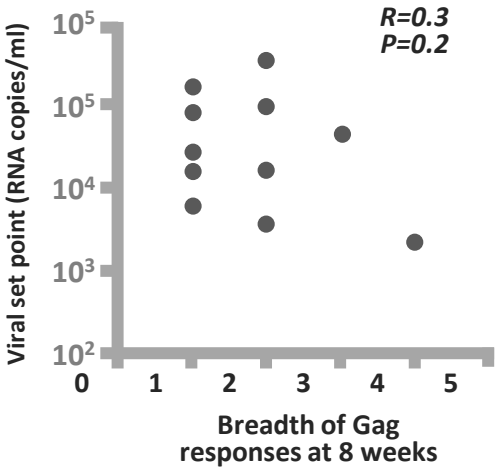
- GWAS and importance of HLA in HIV
- Viral escape can occur that abrogates immune recognition

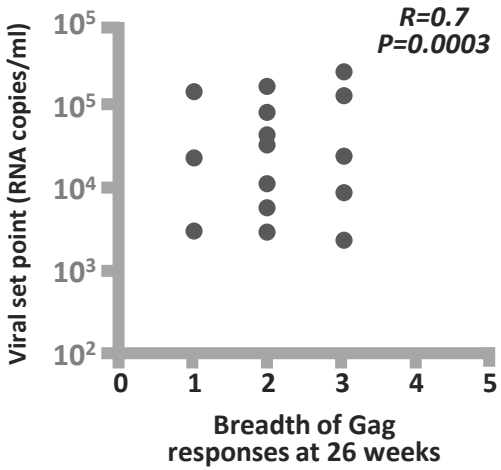
ELISPOT assay



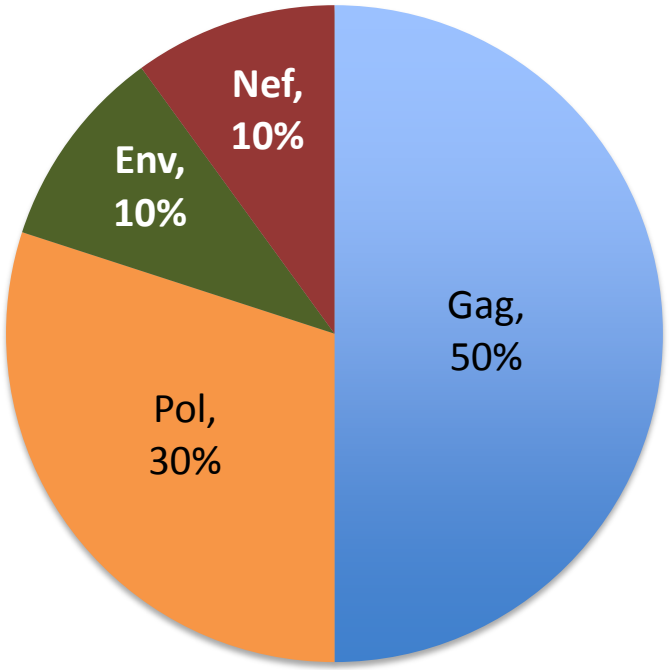
Protein-specificity of CD8 T cell responses and association with viral load

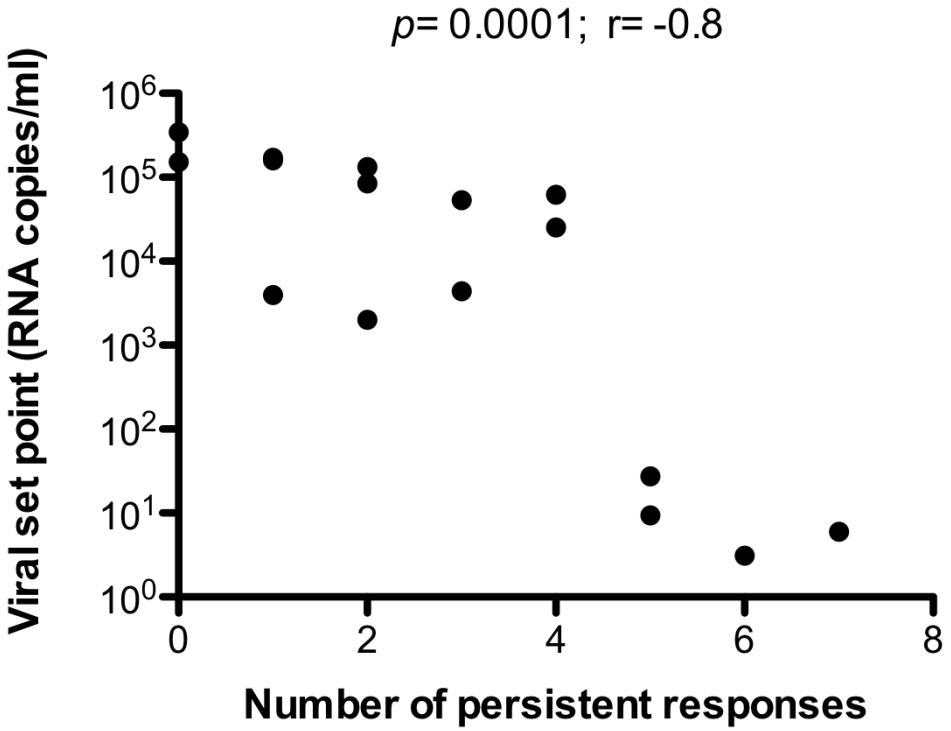






Persistent Gag responses correlate with lower viral load set point



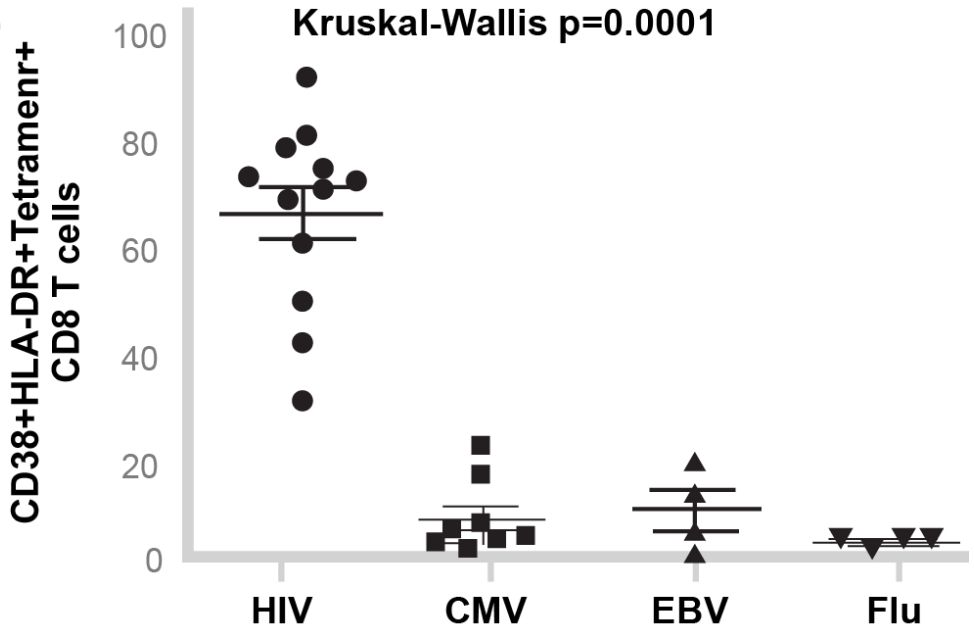


Persistent responses were defined as:

- Responses that persisted over time and
- Were detected in at least 3 time-points 4w, 6w, 8w, 14w, 26w, and 52w post infection

HIV-specific CD8+ T cells are numerous but defective

B



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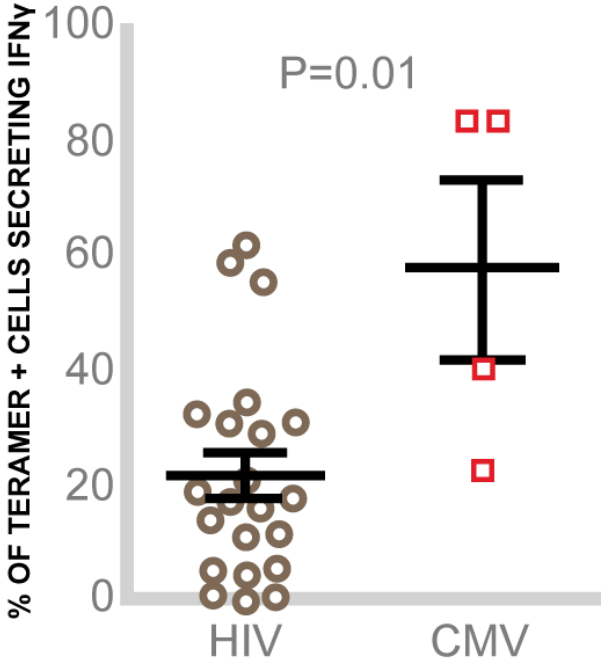


Conclusions II

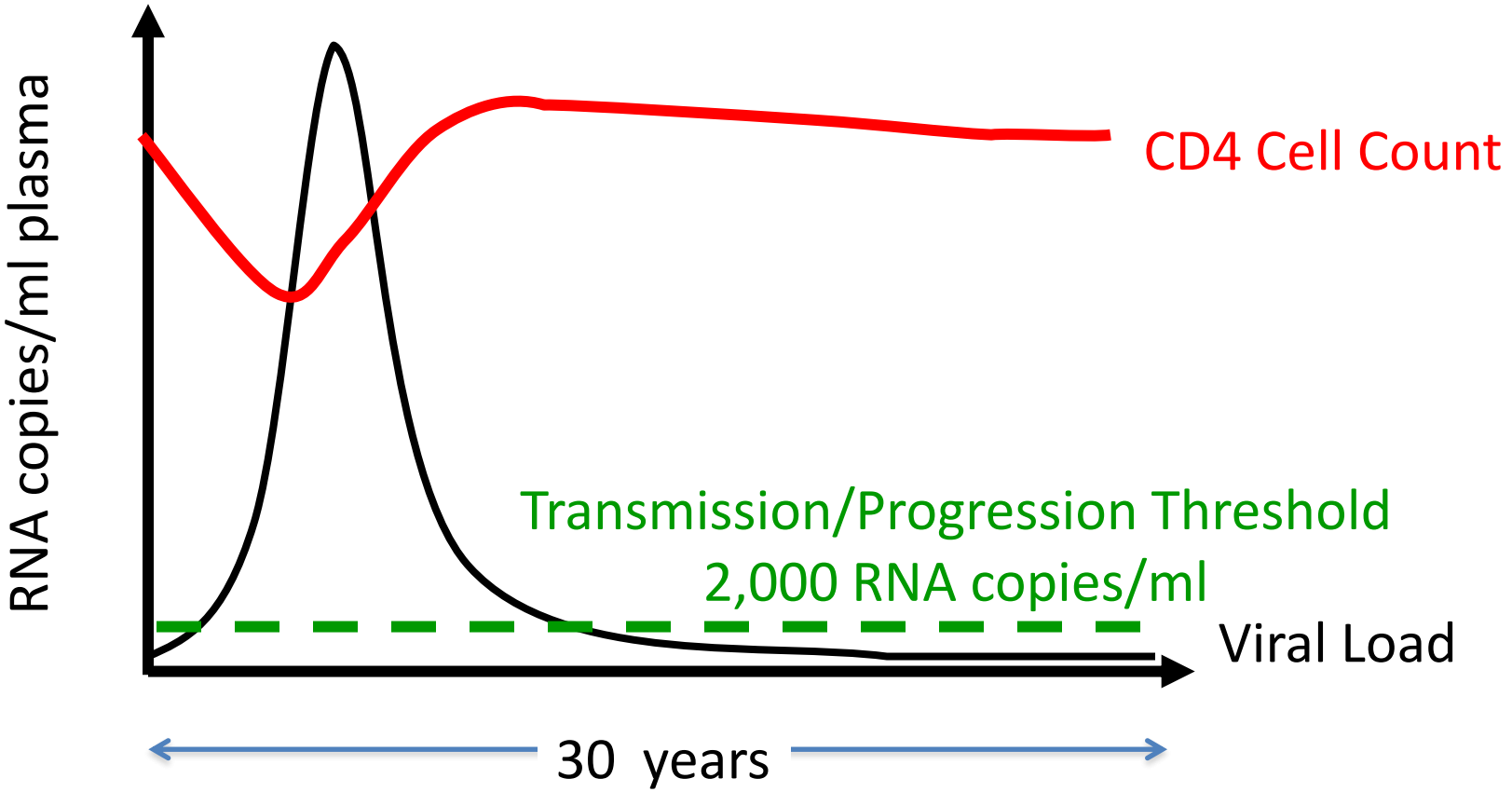
- Nef-specific CD8+ T cell responses are immunodominant in acute HIV-1 infection but do not correlate with viral control.

- Gag-specific immune responses associate with viral control in early (but not acute) HIV-1 infection.

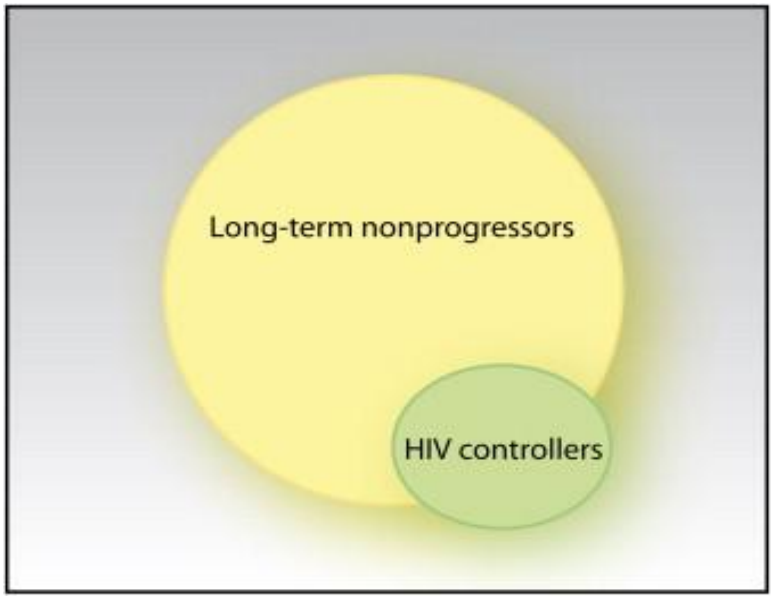
- Limited immunogenicity, transient and defective immune responses may explain the failure of the immune system to contain the virus.

Radebe et al, *JID*, 2011; Radebe et al, *AIDS* 2015 ; Gounder et al, *PLoS One* 2015; Ndhlovu et al, *Immunity*, 2016

HIV controllers: a model of successful viral control?



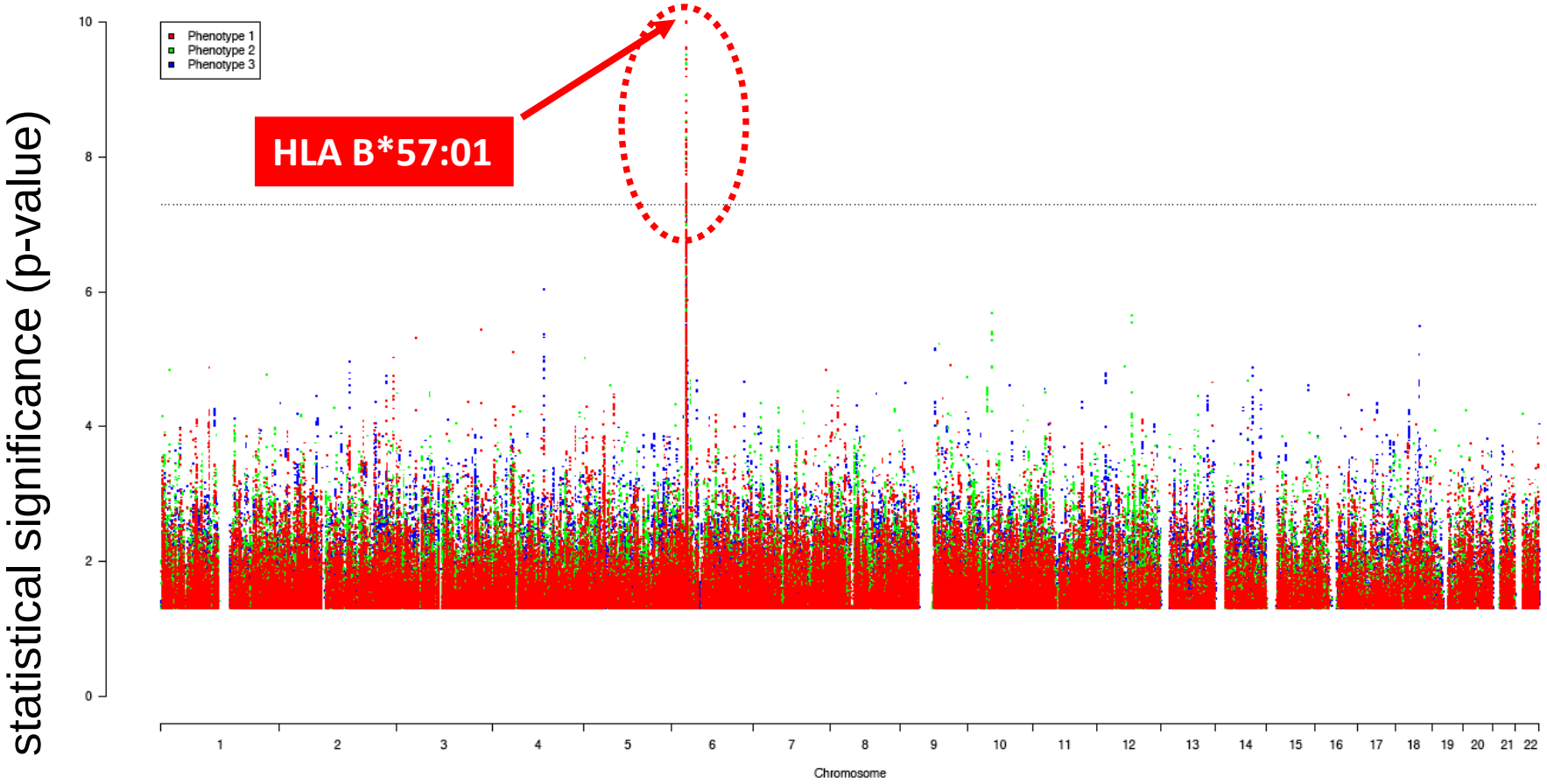
Distinction between elite controllers and long-term non-progressors



- EC defined by VL <50 copies/ml
- LTNP defined by ability to maintain normal CD4 counts for long period
- 5%-15% of infected persons are LTNP
- Less than 0.15% of infected individuals are elite controllers

j.immuni.2007.08.010

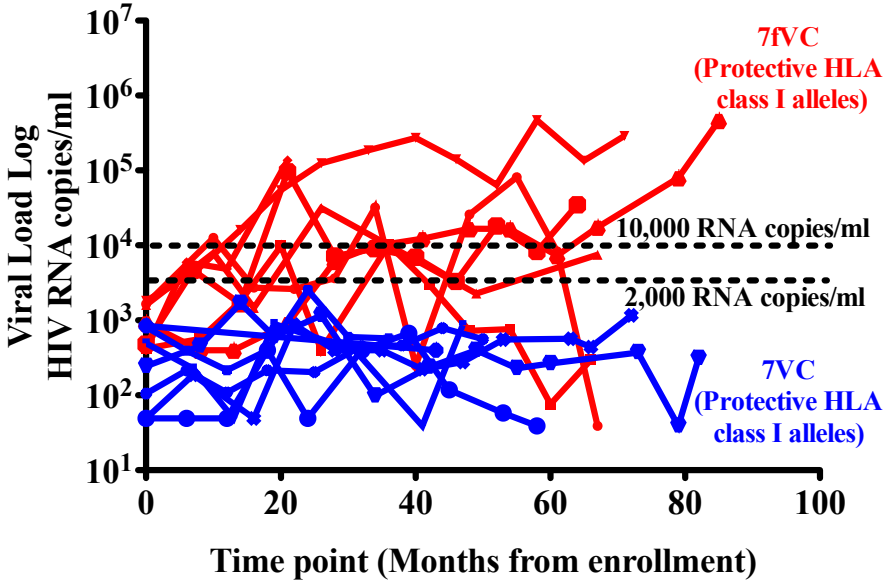
Genome-wide association studies: host HLA is the most significant determinant of outcome



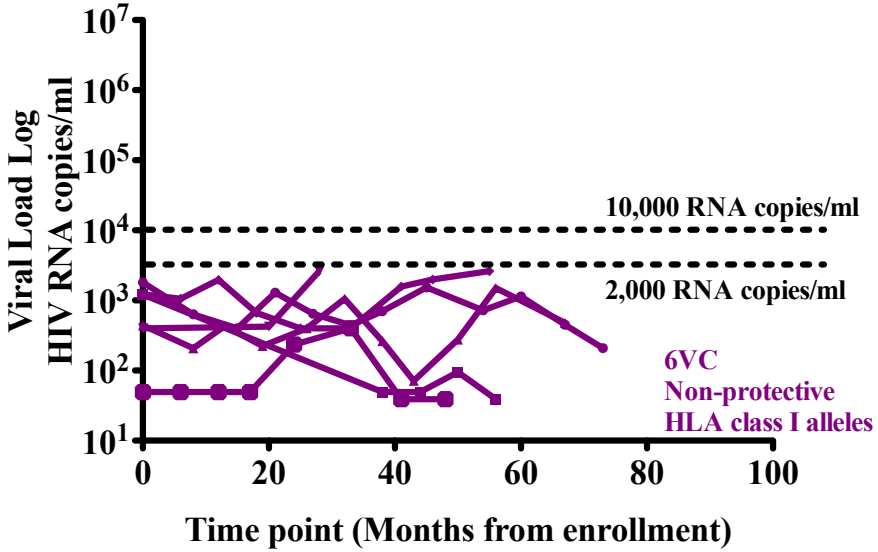
Pereyra et al, *Science*, 2010

Controllers without protective HLA class I alleles more likely to maintain viral control

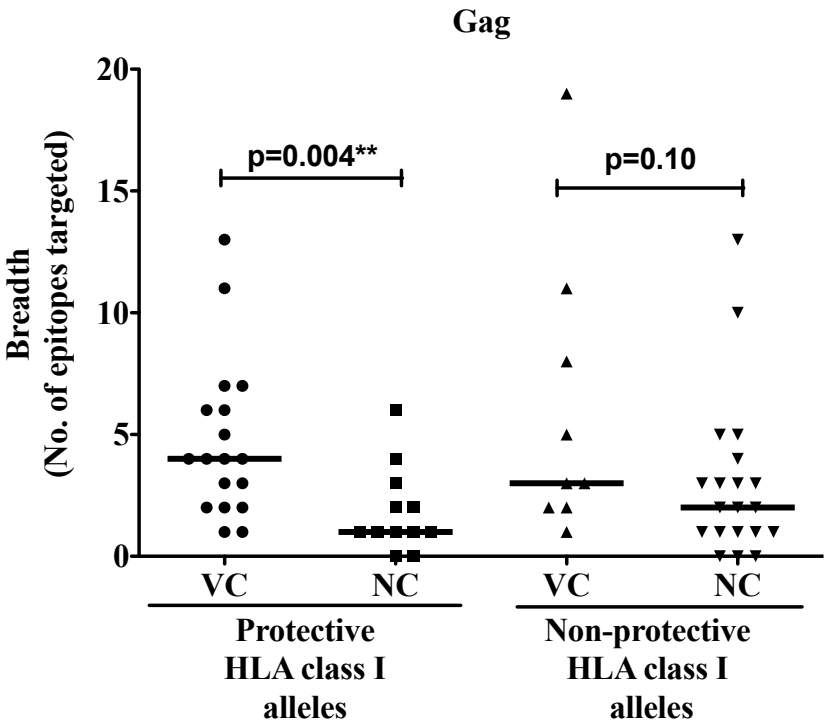
Controllers with protective HLA alleles

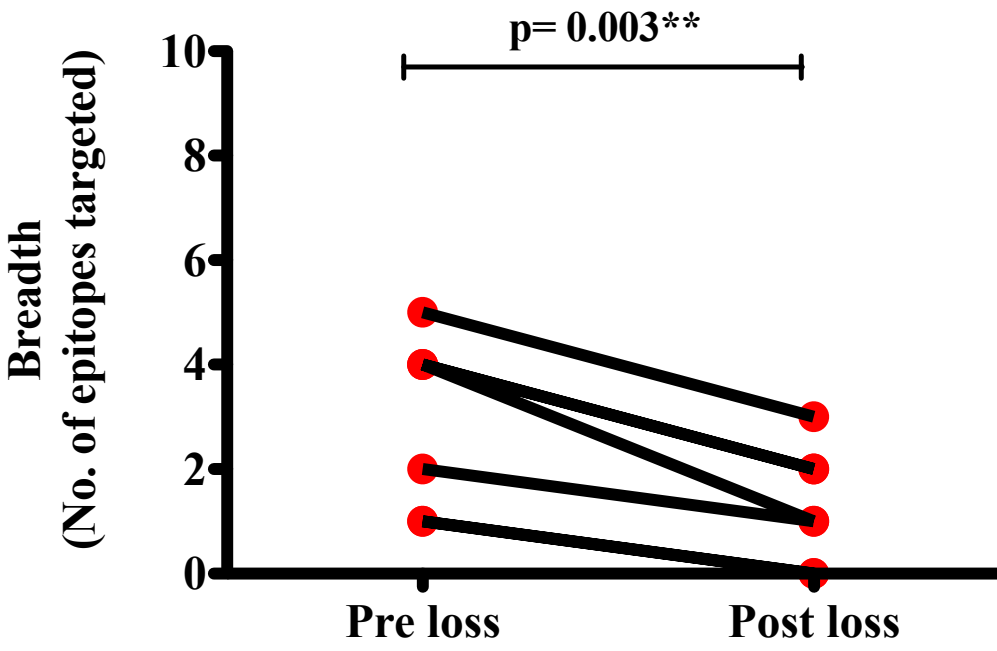


Controllers without protective HLA alleles

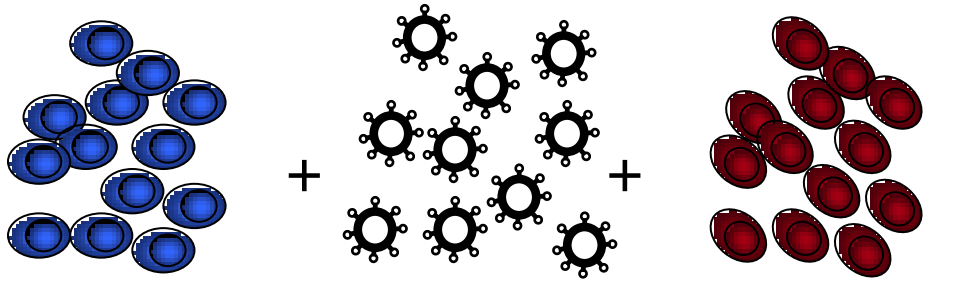


Viremic controllers with protective HLA alleles have broad anti-Gag responses compared to non-controllers





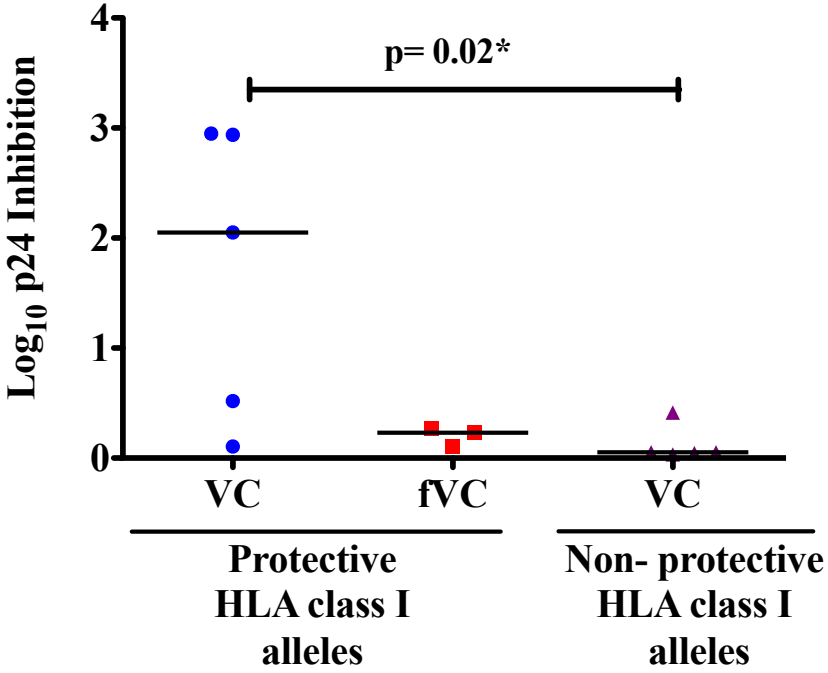
CD8+ T cells from controllers without protective HLA alleles have poor viral inhibition capacity



CD4+ T-cells + HIV + CD8+ T-cells

Co-culture
CD8 and CD4 T-cells
E:T ratio 1:1

Inhibition of HIV Replication measured by p24 in supernatants



Conclusions III

- HIV controllers with protective HLA alleles appear to have a CD8+ T cell-mediated mechanism of control
- Controllers without protective alleles have an alternative, more durable mechanism of HIV control.
- Understanding the mechanisms of control in acute HIV infection and in controllers may lead to novel prophylactic or therapeutic interventions

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