

Genetic determinants of durable control of HIV replication in the absence of antiretroviral therapy

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Background

HIV-seropositive individuals who are able to maintain undetectable to low plasma HIV RNA levels in the absence of antiretroviral therapy should be highly informative for determining the immunologic correlates of HIV control. We have recruited and are now characterizing the genetic determinants of control, as well as the natural history of these rare individuals.

Methods

Three groups were examined:

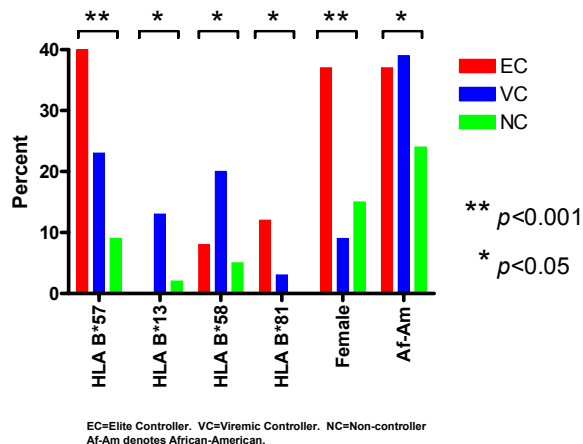
- (1) "Elite controllers (EC)" (n=35):
 - Untreated for >1 year
 - HIV RNA <75 copies/mL for ≥3 determinations spanning >1 year
- (2) "Viremic controllers (VC)" (n=51):
 - Untreated for >1 year
 - HIV 75–2000 copies/mL for ≥3 determinations spanning >1 year
- (3) "Non-controllers (NC)" (n=371):
 - HIV RNA >10,000 copies/mL

Baseline Characteristics

	EC	VC
Plasma HIV RNA (copies/mL)	<75	593
CD4+ T cell count (cells/mm ³)	792	563
Duration of HIV infection (years)	13	11
Duration of follow-up (months)	16	12

Results

- 40% of EC were HLA B*57, compared to 23% of VC and 9% of NC (Fisher's exact test, $p < 0.001$); this effect was independent of race.
- Other HLA alleles that were more common in controllers (EC/VC) vs. NC included: HLA B*13, B*58, and B*81 ($p < 0.05$ for each).
- Neither EC (11%) nor VC (15%) were enriched for the CCR5Δ32 mutation, compared to NC (15%).
- Women represented 37% of EC, 9% of VC, and 15% of NC ($p = 0.001$).
- African-Americans represented 37% of EC, 39% of VC, and 24% of NC ($p = 0.021$).



Results (cont'd)

- Only 1 subject from each group experienced a loss of virologic control during the period of observation, defined as a confirmed increase in HIV RNA of $\geq 0.5 \log_{10}$ above the upper limit defining this group (i.e., an increase to ≥ 237 copies/mL for EC or ≥ 6324 copies/mL for VC).

Conclusions

- HIV seropositive individuals with durable control of HIV replication in the absence of therapy are highly enriched for certain HLA class I alleles, particularly HLAB*57, but not for the CCR5Δ32 mutation.
- However, approximately 35% of these individuals did not exhibit known genetic markers associated with adaptive T cell responses, suggesting that other mechanisms are responsible for their favorable virologic control.