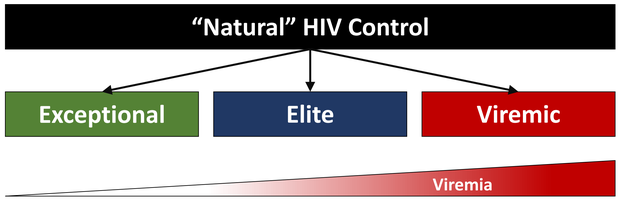
CHARACTERIZING "EXCEPTIONAL" CONTROL AMONG HIV ELITE CONTROLLERS

Michael J. Peluso[1], Peter Burbelo[2], Shreya Kumar[1], Sadie Munter[1], Rebecca Hoh[1], Sulggi Lee[1], Peter W. Hunt[1], Rachel L. Rutishauser[1], Timothy J. Henrich[1], Steven G. Deeks[1]

[1]University of California, San Francisco, CA, USA, [2]National Institutes of Health, Bethesda, MD, USA

BACKGROUND

- Natural control of HIV is a spectrum.
- Elite controllers:
  - Demonstrate substantial variability in their degree and durability of control.
  - Experience increased levels of inflammation and immune activation in many cases.
  - Are often treated with ART for the above reasons.
- Recently, a small number of individuals able to maintain ART-free control for long durations has been described (Mendoza 2012, Canoui 2017, Casado 2020).



- If identified and studied in larger numbers, "exceptional" controllers could inform the cure agenda.

METHODS

- We identified all individuals in the UCSF SCOPE cohort meeting a strict clinical case definition of elite control.

SCOPE "Strict" Elite Control Case Definition
1. Chronic infection without prior ART
2. 3 VL < assay limit, spanning 1 year
3. No VL >200 in preceding 2 years
4. ≥50% of last 3 VLs below LOD
5. ≥50% of all VLs in last 2 years below LOD

n=352 putative controllers → n=73 met EC criteria at least one time point

- For these analyses, we defined "exceptional" controllers as individuals with undetectable cell-associated HIV DNA on analysis of ~9 million PBMCs.
- We hypothesized that exceptional controllers would exhibit lower amounts of immunologic decline, T cell activation, and clinical progression compared with typical elite controllers in the cohort.

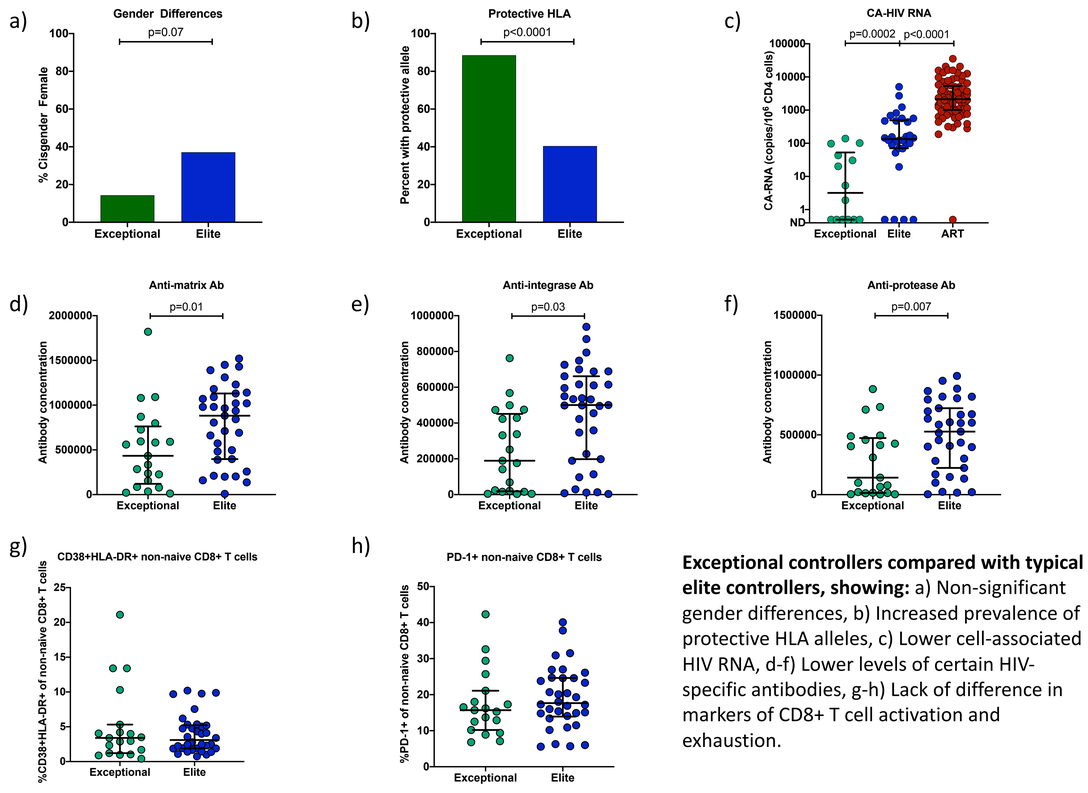
"Exceptional" controllers are a newly recognized subset of individuals who naturally control HIV infection.

"Exceptional" controllers are highly enriched for protective HLA alleles, arguing that CD8+ T cells may mediate such control.

"Exceptional" controllers maintain higher CD4/CD8 ratios over time and appear less likely to progress than typical elite controllers.

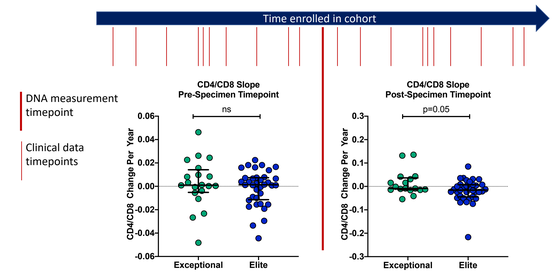
Further study is needed to evaluate markers of inflammation, viral activity in tissues, and the benefits of ART in these individuals.

RESULTS



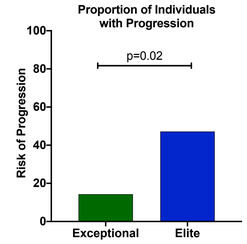
Exceptional controllers compared with typical elite controllers, showing: a) Non-significant gender differences, b) Increased prevalence of protective HLA alleles, c) Lower cell-associated HIV RNA, d-f) Lower levels of certain HIV-specific antibodies, g-h) Lack of difference in markers of CD8+ T cell activation and exhaustion.

RESULTS, CONTINUED



Exceptional controllers demonstrate stable CD4/CD8 ratios compared with elite controllers. Slopes calculated using mixed-effects linear regression from timepoint at which the reservoir was measured.

Progression defined as:
1. Loss of elite control
   - Any plasma HIV RNA >200 copies
   - <50% of plasma HIV RNA above LOD
2. Initiation of ART for frequent "blipping"
3. Initiation of ART for CD4 decline



Exceptional controllers are less likely to progress than elite controllers. Low reservoirs during a control timepoint may contribute to the exceptional control definition.

CONCLUSIONS

- We identified a subset of controllers with very low HIV DNA levels, who had low antibody levels, and lower risk of clinical progression. These individuals were enriched for certain HLA alleles, arguing that CD8+ T cell responses may mediate such control.
- Exceptional controllers appear less likely to progress than typical elite controllers. Further evaluation of inflammation, viral activity in tissues, and the benefits of ART in these controllers is needed.
- Careful consideration should be given to how best to define this new clinical phenotype.

ACKNOWLEDGEMENTS

- We are grateful to the research participants.

Contact: Michael Peluso, MD
michael.peluso@ucsf.edu