Exceptional HIV Elite Controllers

Session: Let's talk about HIV Cure

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Conflict of interest disclosure

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Extrem Cases of HIV-1 Disease Progression

- Rapid Progressors
- Normal Progressors
- HIV Controllers
- Viremic Non-Progressors
- < 1%

Angel Bayon
Track A
#EPA011
Are elite controllers a model for a functional cure?

- Is it the virus?
  - Reservoirs, evolution, virus intactness?

- Is it the host?
  - Genetics, immunology, immuno-genetics?

- But elite controllers are heterogeneous in terms of long-term clinical, virological and immunological progression

- Are SOME elite controllers a model for a functional cure?
  - Undetectable plasma viremia and normal CD4 T-cell counts for >10 years appear to represent a very promising model
Extrem Cases of HIV-1 Disease Progression

- Exceptional Elite Controllers
- Rapid Progressors
- Normal Progressors
- HIV Controllers
- Viremic Non-Progressors
- < 1%
“Exceptional” HIV Elite Controllers (EEC) 
the limitation of definitions ...

- People with HIV that spontaneously control viral replication in absence of immune dysfunction
- No disease progression in absence of antiretroviral therapy
- Extraordinarily low HIV burdens
- Comparatively weak immune response
- Long-term control: >10-25 years
- Partially reactive for HIV-specific antibodies
Years after HIV diagnosis

- Casado et al. Sci Rep Feb 2020 (EEC-3) - 29 M
- Casado et al. Sci Rep Feb 2020 (EEC-56) - 28 W
- Mendoza et al. Blood May 2012 (#4) - 28 W
- Jiang et al. Nature Sep 2020 (EC-2)
- Mendoza et al. Blood May 2012 (#2) - 12* M
- Jiang et al. Nature Sep 2020 (EC-1) - 12
- Mendoza et al. Blood May 2012 (#1) - 6 M

50% Women

Years at the time of publication
Light blue denotes temporal antiretroviral therapy
* No subsequent follow up after publication

Mendoza et al. 2012; Casado et al. 2020; Jiang et al. 2020; Turk et al. 2022
Clinical evolution

- Median of 24 (range 6–64) plasma viral load tests
  - Always below the limit of detection of contemporary assays
  - Except for ≤2 non-consecutive blips below 400 cps/ml
- Ultrasensitive plasma viremia / SCA below 0.4 cps/ml
  - Except for 1 sample of 2 cps/ml
- Median absolute CD4+ T cells in last determination of 921 (range 529-1488)
- Ratio CD4/CD8 always >1
  - Except for the Esperanza’s case in whom is variable
## Host Genetic Determinants

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<th>#3</th>
<th>#4/SFO</th>
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# Proviral DNA and qVOA

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<td>Proviral DNA</td>
<td>6.56</td>
<td>25.2</td>
<td>n.a.</td>
<td>IPDA⁻</td>
<td>27.09</td>
<td>8.75</td>
<td>10.05</td>
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<td>copies/E6 cells</td>
<td>PBMC</td>
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<td>14E6 rCD4⁺</td>
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<td>&lt;0.004</td>
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<td>28E6 tCD4⁺</td>
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<td>150E6 rCD4⁺</td>
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<tr>
<td>copies/E6 cells</td>
<td>n.a.</td>
<td>2.8cp</td>
<td>1.9cp</td>
<td>HIV DNA⁻ in 4E6 CD4⁺ from rectum &amp; ileum*</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>placenta (neg)</td>
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<td>colon E6/CD4</td>
<td>colon E6/CD4</td>
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qVOA: quantitative Viral Outgrowth Assay; rCD4⁺: resting CD4⁺; tCD4⁺: total CD4⁺; n.a.: no available
* , a previous sample from 2012: <2.6 copies/10⁶ cells in colon, and 42.4 copies/10⁶ cells in ileum
Mendoza et al. 2012; Casado et al. 2020; Jiang et al. 2020; Turk et al. 2022
Near-full length virus sequencing

337 amplification attempts with 12.4E6 CD4+ and 6.4E6 PBMCs

Casado et al. 2020
Viral Evolution and Genetic Variability

- Very restricted genetic diversity: 0.010 ± 0.003 s/n
- Almost null viral genetic evolution

Figure 2. Genetic variability and evolutionary dynamics of viral populations (A) Phylogenetic trees with env gene sequences of the individuals during follow-up. The evolutionary history was inferred in trees by using the Maximum Likelihood method based on the General Time Reversible model. The percentage of trees in which the associated taxa clustered together with values over 70% is shown next to the branches. Initial tree for the heuristic search was obtained by applying the Neighbor-Joining method to a matrix of pairwise distances estimated using the Maximum Composite Likelihood approach. A discrete Gamma distribution was used to model evolutionary rate differences among sites (4 categories). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. Evolutionary analyses were conducted in MEGA6. Different colors were used to indicate the sampling time. (B) Genetic variability analysis of samples from different groups of HIV-1 individuals with a controlled infection (see Materials and Methods).
Cloned Envs from EEC allowed functional characterization of the initial events of the viral infection:

- Ineffective binding to CD4 and the subsequent signaling activity to modify actin/tubulin cytoskeletons

Low fusion
- Deficient entry and infection capacity
Cellular Immune Responses

- HIV-specific T-cell responses were present
  - Comparatively higher and greater polyfunctionality than those from PWH on ART
  - Similar to other LTNP/EC

- Host CD4⁺ T cells are susceptible to infection with R5 or X4-tropic HIV
- Host CD8⁺ T cells are effective in suppressing viral viral replication ex vivo

Mendoza et al. 2012; Casado et al. 2020
Humoral Immune Responses

- All weakly reactive, either Western Blot or ELISA
  - But superior to 2 cases of stem-cell transplant with CCR5Δ32/Δ32 donor cells (IciStem cohort)
  - Viral antigens and/or truncated viral proteins could be generated from defective genomes
Inflammation Biomarkers

- Similar to those in the blood of healthy donors
  - Innate immune responses seem to be relatively normalized

- Analyses in greater number of subjects is required
Proviral HIV intactness and chromosomal location

*distinct proviral reservoir configurations in natural viral control*

Is the HIV provirus intact?

Where does HIV integrate in the genome?

Breakthroughs on the SFO and Esperanza cases

Descriptive data on EEC → Mechanistic data on EEC

Bruce Walker, Steven Deeks, Janet Siliciano, Robert Siliciano

Near-full length virus sequencing

- Full-Genome Individual Proviral Seq
- IPDA
- Viral outgrowth assay

Essentially ... Defective Proviruses

- San Francisco's
- Esperanza's

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<th>Year</th>
<th>5' LTR</th>
<th>gag</th>
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- Full-Genome Individual Proviral Seq
- IPDA
- Viral outgrowth assay

Conclusions

- Consistently low, and apparently defective, viral DNA reservoir
- Practically null viral genetic evolution and extremely low complexity of the viral populations → absence of viral replication for >25 years
- Low population size and viral diversity are associated with low replication and viral fitness
- Contribution of host genetic factors and cellular-adaptive immune responses

Hypotheses:
- Primary infection might have occurred with a low fitness viral founder strain
- Initial innate immune responses might have shaped the selection of an unfit virus

Is it possible to induce a permanent control of HIV-1 pathogenesis?
Future directions

- Current cases on follow up (years)

Argentina, Belgium, Spain, United States

jmpicado@irsicaixa.es

*, unpublished cases
Future directions

Hematological Stem Cell Transplant

Exceptional Elite Controllers

Extremely low viral reservoir (LoViReT)

Adam Castillejo  
London Patient  
4.5 years

Düsseldorf Patient  
3.5 years  
Non-CCR5Δ32 donors  
on ART

Δ32  
Donor

HIV+  
Stem cells 

ICISTEM

HIV+  
cured HIV patient

HIV resistent


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