Loss of Virological Control 32 Years After HIV-1 Diagnosis in an Exceptional Elite Controller

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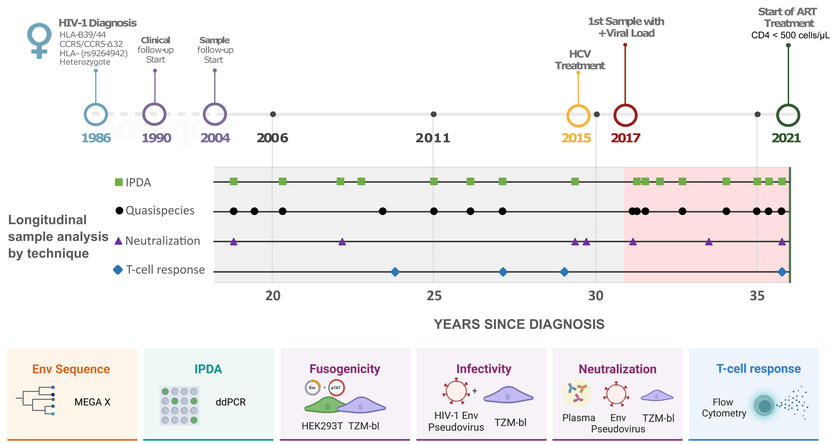
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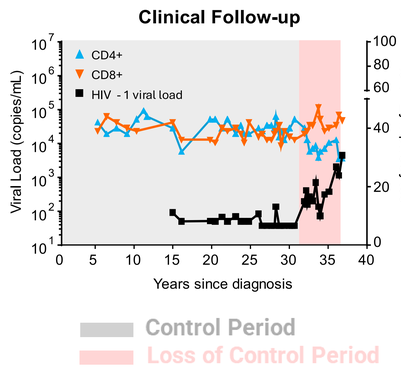
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BACKGROUND

HIV-1 Exceptional Elite Controllers (EEC) maintain undetectable viremia and halt disease progression more than 20 years after diagnosis in the absence of treatment and may be considered as functionally cured. However, cases of EEC losing control have been described. To understand mechanisms behind loss of control, we performed a detailed, longitudinal characterisation of the HIV-1 reservoir, viral evolution and immune (B- and T-cell) response in an EEC that unexpectedly lost viral control 32 years after diagnosis.

METHODS





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Persistent virological control is not necessarily associated with a steady-state scenario, but may be highly dynamic and involve both virological and immunological changes that will define the outcome of exceptional control.

RESULTS

1. Longitudinal analysis of the viral reservoir showed dynamic changes both in size and composition during the EEC follow-up period.

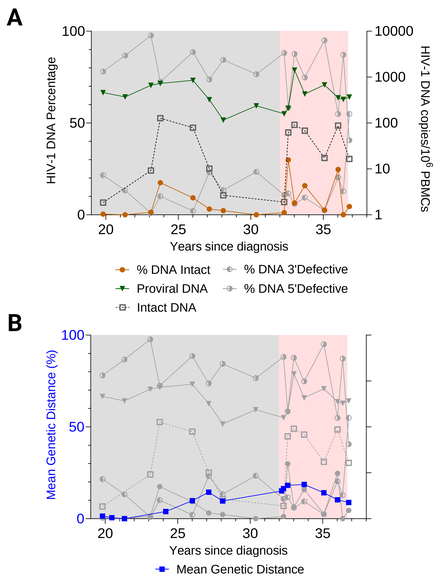


Figure 1. Follow-up of HIV-1 DNA reservoir integrity. (A) The percentage of intact, 3'defective and 5'defective HIV-1 DNA was determined by Intact Proviral DNA assay (IPDA). Proviral DNA was determined by ddPCR. Absolute Intact DNA was extrapolated from IPDA and proviral DNA data. The right Y-axis is displayed on a logarithmic scale. Light grey box indicates EEC period during follow-up. (B) Mean Genetic distance (substitutions per site, %).

2. Envelope sequence diversity increases 10 years prior loss of control and is associated with increased functionality.

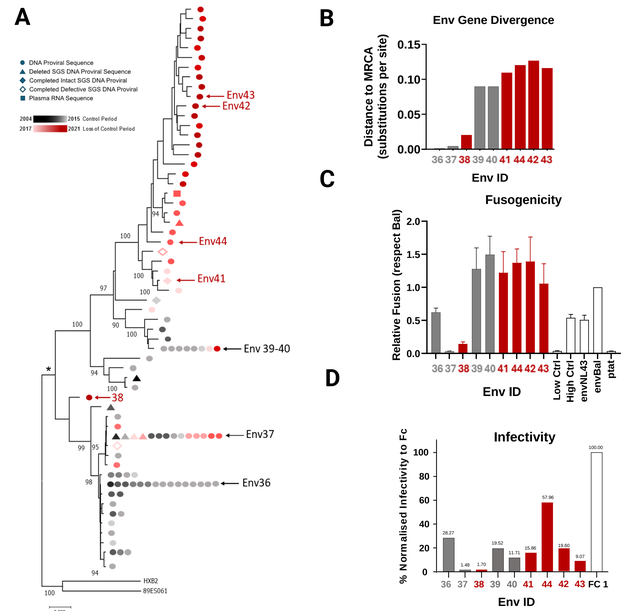


Figure 2. Genotypic and Phenotypic characterization of isolated HIV-1 EEC Env Clones isolated during the control (grey) or loss of control period (red). A) Phylogenetic Tree of the isolated Env sequences. Their MRCA is marked by *. The evolutionary history was inferred using the Neighbour-Joining method and evolutionary distances calculated using the Poisson correction method. The % of trees where the associated taxa clustered with values >90% is displayed next to the branches. B) Env distance to the MRCA. C) Fusogenic activity of the isolated Env clones relative to Bal as 100% of infection. Reference HIV-1 viral strains, a low and a high fusogenic Env and ptat were used as controls . Values show the Mean +/- SEM of four independent experiments (n=4). D) Infectivity of pseudoviruses bearing the isolated EEC Env or the reference Env FC 1.

3. Neutralization of contemporaneous viruses is observed during the EEC period and reduced after the loss of EEC status.

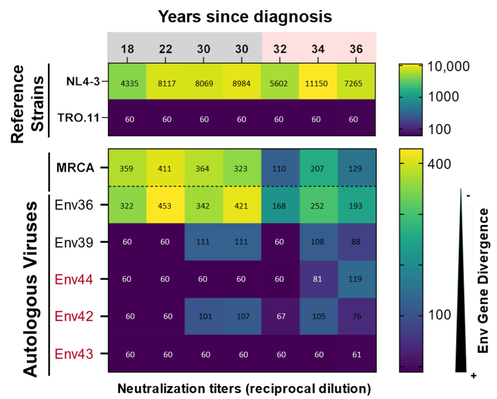


Figure 3. HIV-1 EEC plasma samples neutralization titer Heatmap (reciprocal dilution) against reference strains (NL4-3 and TRO.11), a MRCA node* and autologous Env pseudoviruses. Plasma samples and autologous Envs from before and after loss of control were analyzed. The limit of quantification is ≤60. **Node from an EC cluster in a phylogenetic tree containing EC Env nucleotide sequences from Spanish samples.*

4. Gag-specific T-cell memory responses fluctuate during the control period and decay prior loss of control.

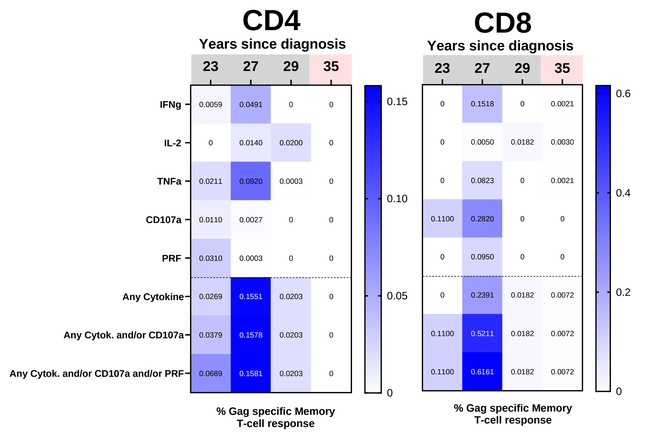


Figure 4. Gag specific Memory T-cell response (%) at different timepoints since diagnosis for different cytokines, CD107a and perforin (PRF). Cells expressing the individual markers are shown on the top. Below the dotted line we show the cumulative specific response of any of the markers, but it does not indicate polyfunctionality.

CONCLUSIONS

Loss of exceptional control 32 years after diagnosis was preceded by:

- **Dynamic changes in viral reservoir**
- **Increased Env diversity and functionality**
- **Reduced neutralization of contemporaneous viruses**
- **Fluctuations in T-cell responses**

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ECRIS: AIDS Research Network HIV-controllers Cohort

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