
Regain of Viremic Control after HIV-1 Superinfection in a Long-term Elite Controller

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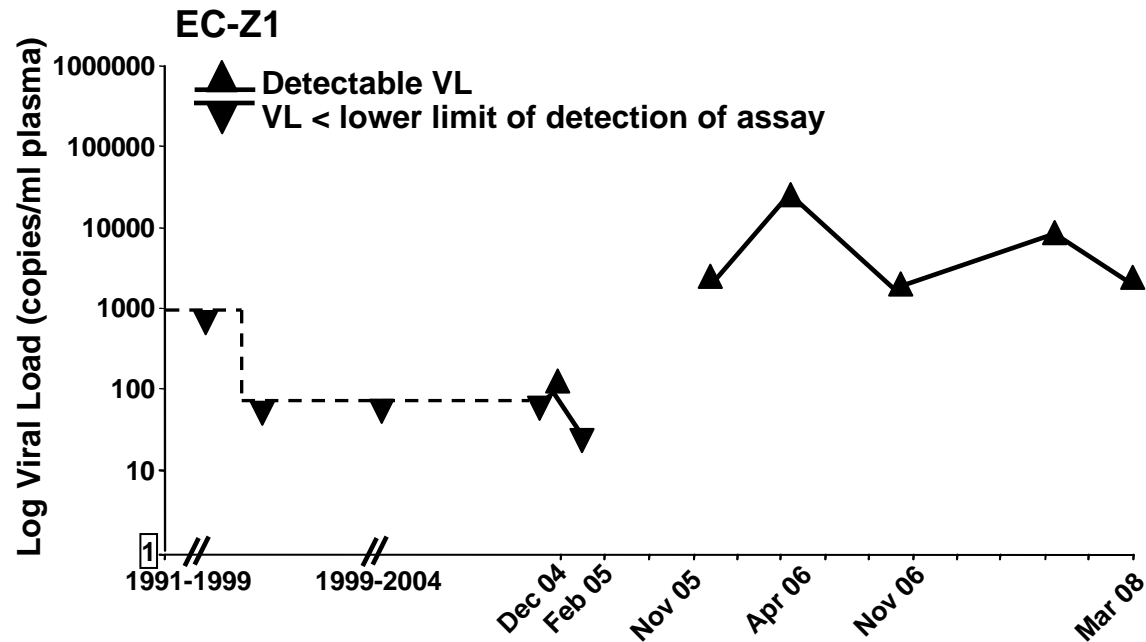


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Characteristics of Elite controller EC-Z1

- Time of infection 1984-1990
- Completely positive HIV-1 Western Blot (1990)
- Always normal CD4 T cell count (range 642-1036)
- No antiviral therapy
- No detectable HIV-1 RNA (<5 copies/ml plasma)
- No detectable replication competent virus in resting CD4 cells
(“latent reservoir” <0.1 /10⁶ cells)
- No detectable proviral DNA in routine diagnostic testing
(<1 copy proviral DNA/10⁵ cells)
- CCR5 wt/wt genotype
- HLA-A 01/03, HLA-B 3501/5701, HLA-C 04/06

Viral load in plasma in EC-Z1



Rise in viral load in EC-Z1 due to loss of control or superinfection?

-Unprotected homosexual contact with steady partner (Z2) for >15 years without transmission of HIV-1

-New partner (Z3) since spring 2005 (first only partner of EC-Z1, later in triangle relationship with both EC-Z1 and Z2)

-August 2006: Z2 seropositive

Sampling dates for HIV-1 env and gag sequencing

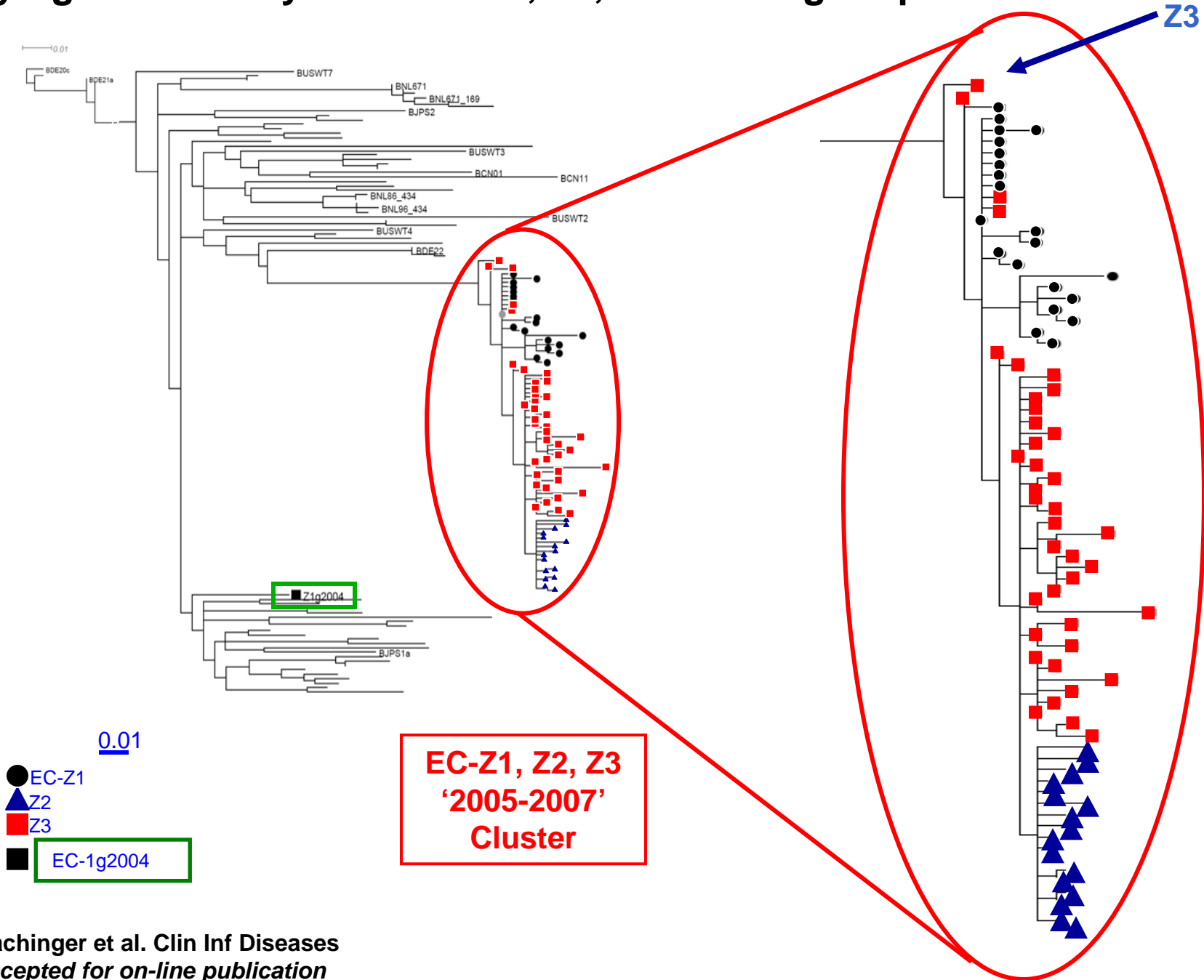
| Z1 | Z2 | Z3 |
|------------|----------|-----------|
| Dec 2004 | | |
| | | May 2005 |
| | | Sept 2005 |
| Nov 2005 | | Dec 2005 |
| Apr 2006 | | Apr 2006 |
| Nov 2006 | Oct 2006 | |
| | Jan 2007 | Febr 2007 |
| | May 2007 | |
| Oct 2007 | Nov 2007 | |
| March 2008 | | Jan 2008 |
| May 2008 | | |

Small gag fragment from patient DNA

Sequences from RNA in plasma and from replication competent clonal HIV-1 variants

Sequenced from RNA in plasma only

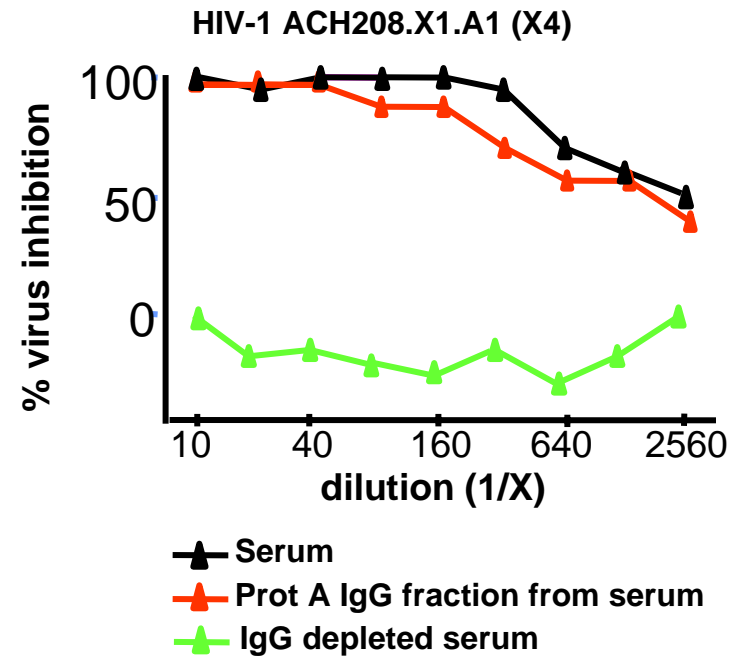
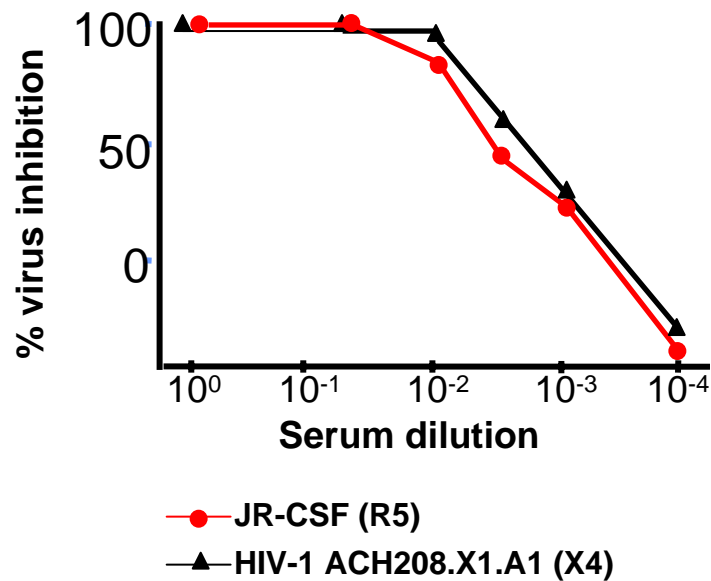
Phylogenetic Analysis of EC-Z1, Z2, and Z3 Gag Sequences from 2004-2007



Conclusions I

- HIV-1 gag sequences from EC-Z1 obtained after start viremia did not cluster with a EC-Z1 gag sequence from 2004 (*Z1gag2004*) but did cluster with HIV-1 sequences from his new partner Z3 (and his steady partner Z2) in phylogenetic analysis.
- Z3 gag sequences are ancestral to the EC-Z1/Z2/Z3 sub-cluster, implicating superinfection of EC-Z1 by Z3.
- Source for infection of Z2 undefined (either EC-Z1 or Z3).

Antibody-Mediated HIV-1 Neutralization by EC-Z1 Serum



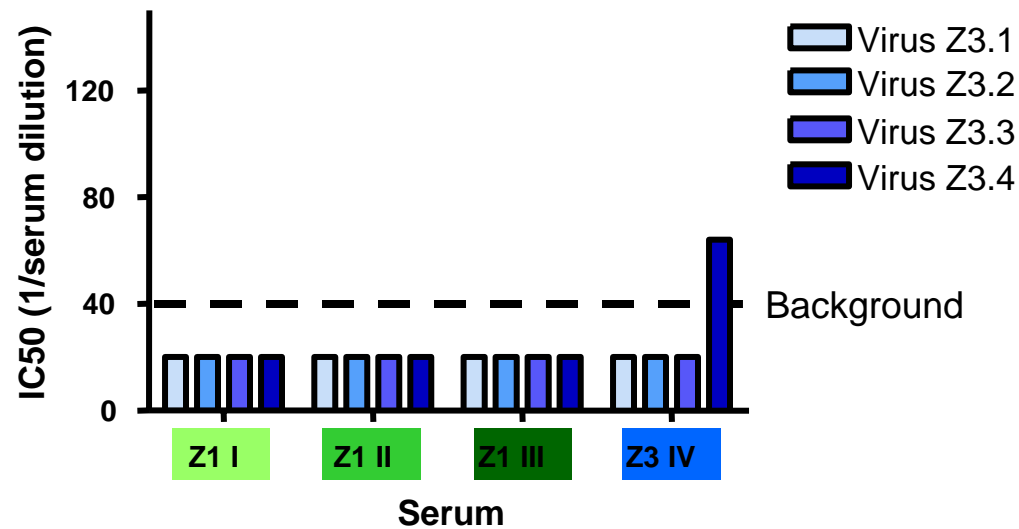
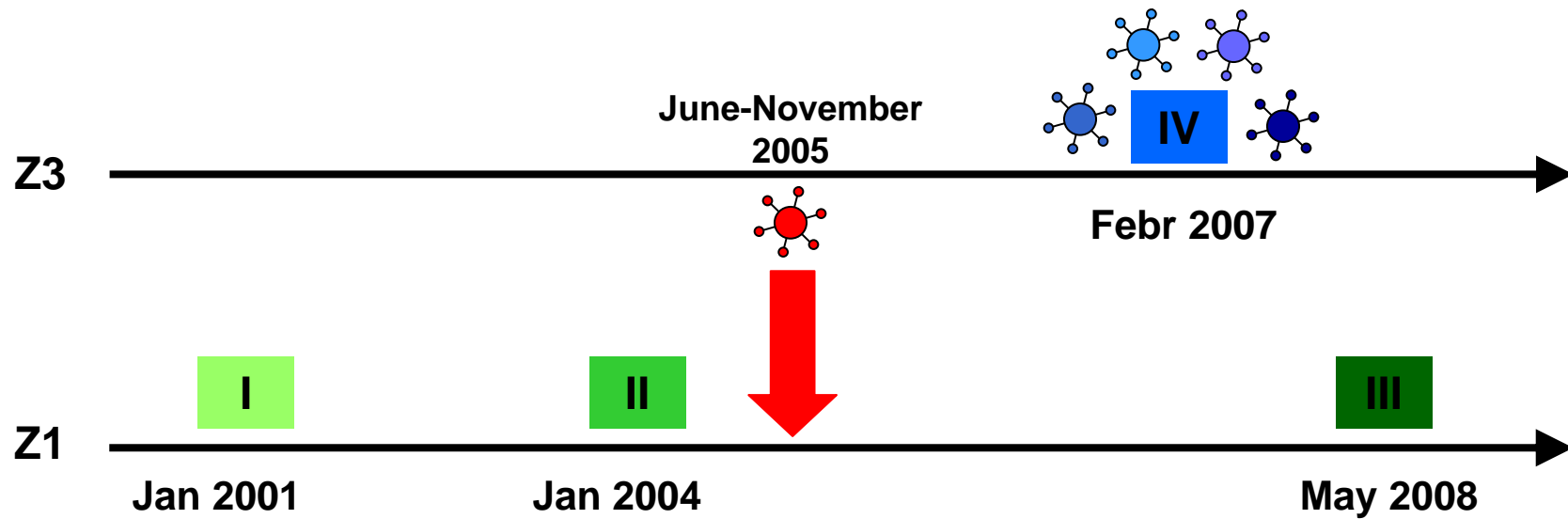
Conclusion:

EC-Z1 has serum neutralizing activity (IgG fraction) against an R5 and X4 HIV-1 variant

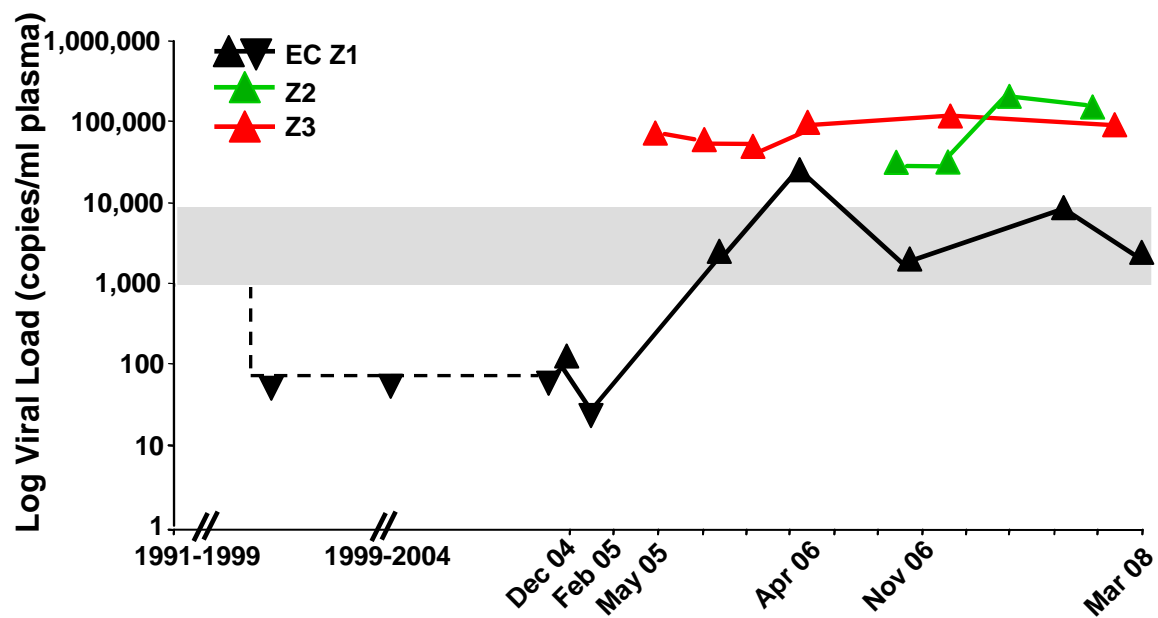
Question:

does EC-Z1 have serum neutralizing activity against superinfecting HIV-1 from Z3?

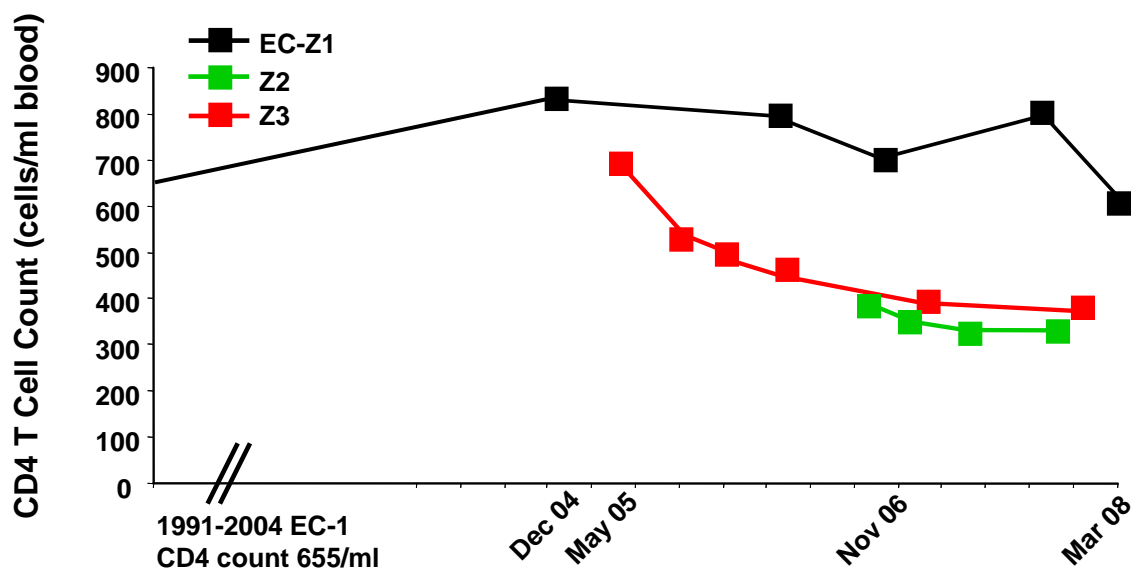
No neutralization of Z3 virus by EC-Z1 sera



HIV-1 load in plasma in EC-Z1 and partners



CD4 T cell counts in EC-Z1 and partners



What determines regain of relative viremic control in EC-Z1?

Summary

- **Elite Controller Z1 superinfected by new partner Z3, after at least 14 years of elite control over first HIV-1 infection**
- **HIV-1 superinfection of an elite controller in the face of functional HIV-specific CD8+T cells (data not shown)**
- **No serum neutralizing activity against HIV-1 from Z3 in EC-Z1 (explains lack of protection?)**
- **EC-Z1 seems to control the superinfecting HIV-1 variant, while Z2 and Z3 who are infected with similar HIV-1 variants, show signs of a progressive disease course**
 - **Reduced in vitro HIV-1 susceptibility of EC-Z1 PBMC as compared to healthy donor PBMC**
 - **HIV-1 variants from EC-Z1 seem to have attenuated phenotype (No deletions in any of the accessory genes, gag, pol, env)**

Conclusions

- **Differential clinical course of infection in three individuals infected with the same HIV-1 variants supports a role for host factors in protection from disease progression in EC-Z1**
- **Host factors that can protect from disease progression may not protect from HIV-1 superinfection.**
- **The exact mechanism by which EC-Z1 re-establishes relative control over viremia after superinfection remains to be established.**

Contributors

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