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

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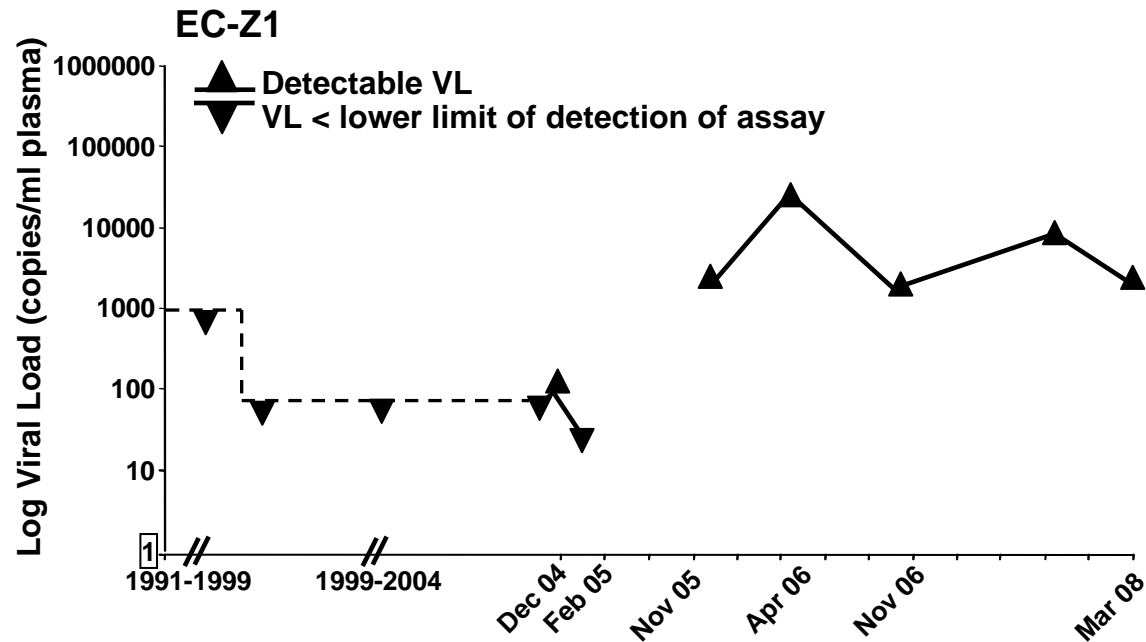
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# Characteristics of Elite controller EC-Z1

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- 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 /10<sup>6</sup> cells)
- No detectable proviral DNA in routine diagnostic testing  
(<1 copy proviral DNA/10<sup>5</sup> 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

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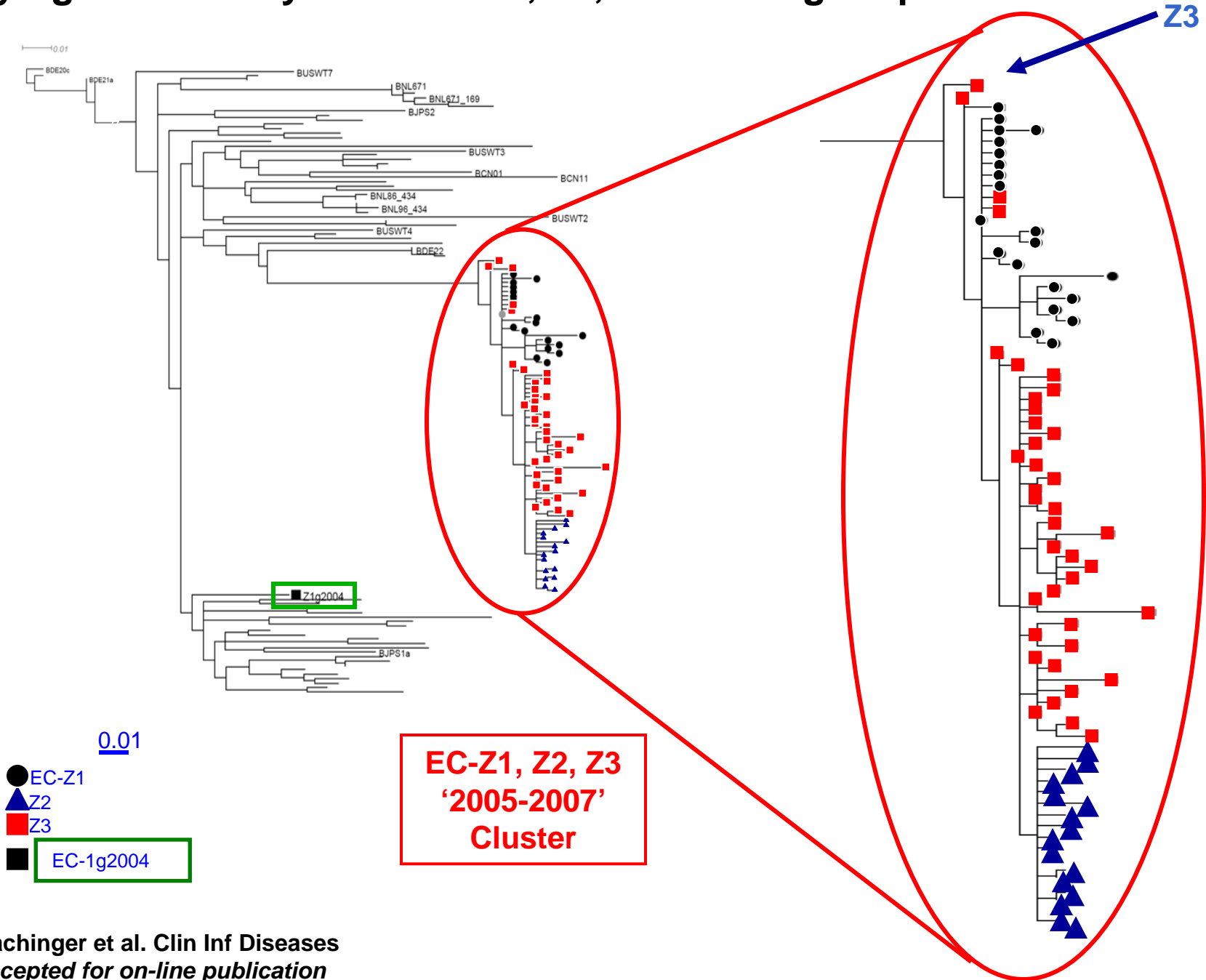
Z1	Z2	Z3
Dec 2004		
		May 2005
		Sept 2005
Nov 2005		Dec 2005
Apr 2006		Apr 2006
Nov 2006	Oct 2006	
	Jan 2007	Febr 2007
	May 2007	
Oct 2007	Nov 2007	
March 2008		Jan 2008
May 2008		

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

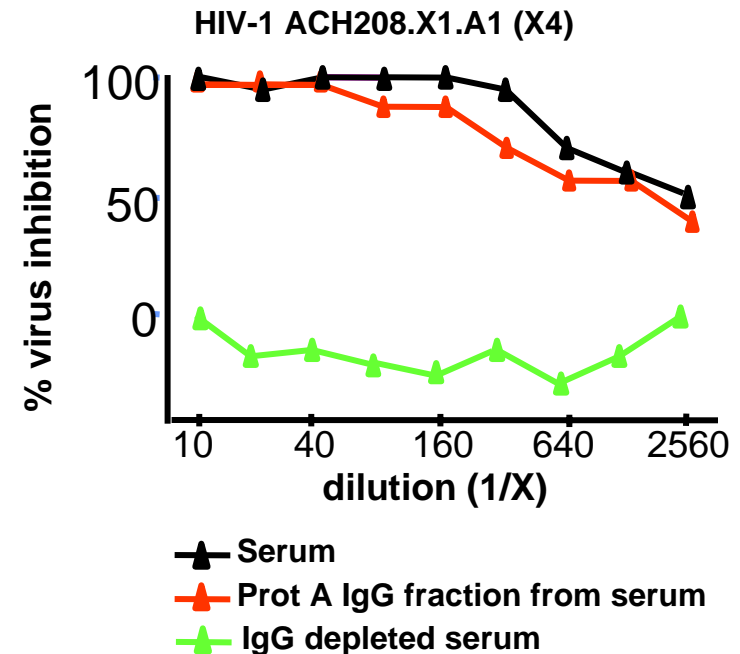
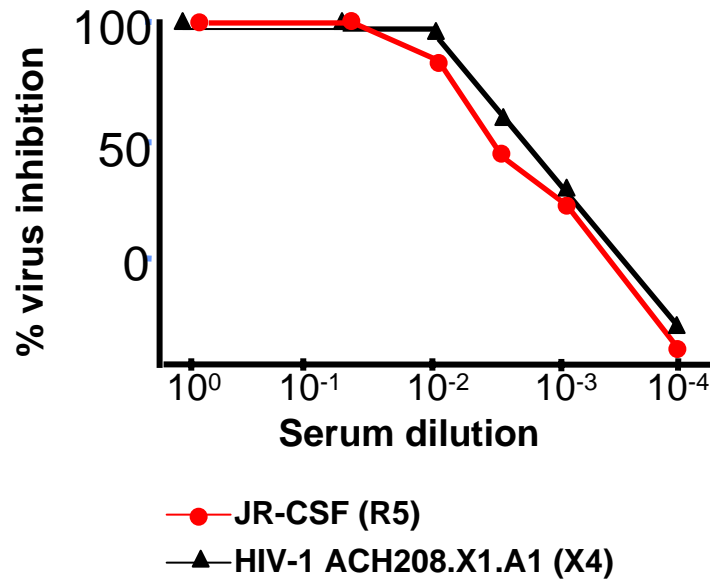


# Conclusions I

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- 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



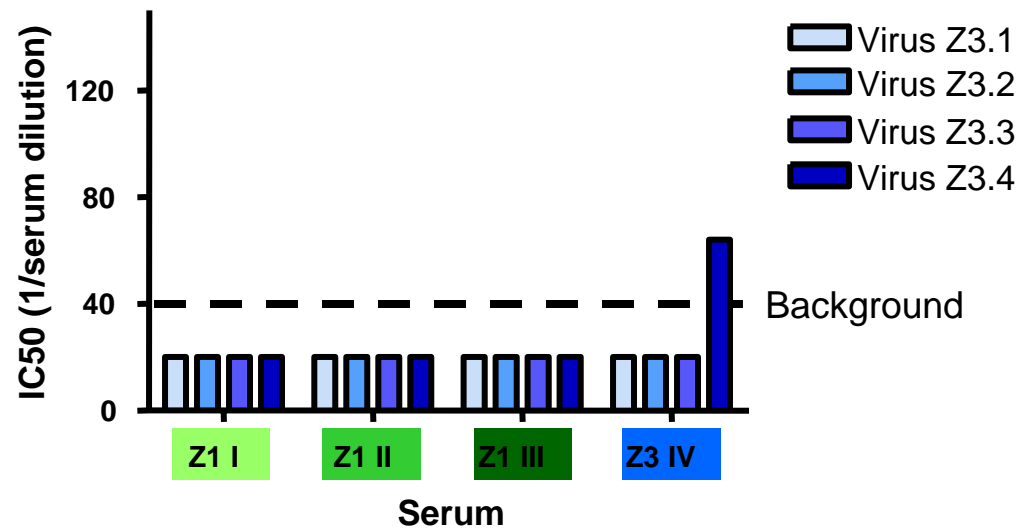
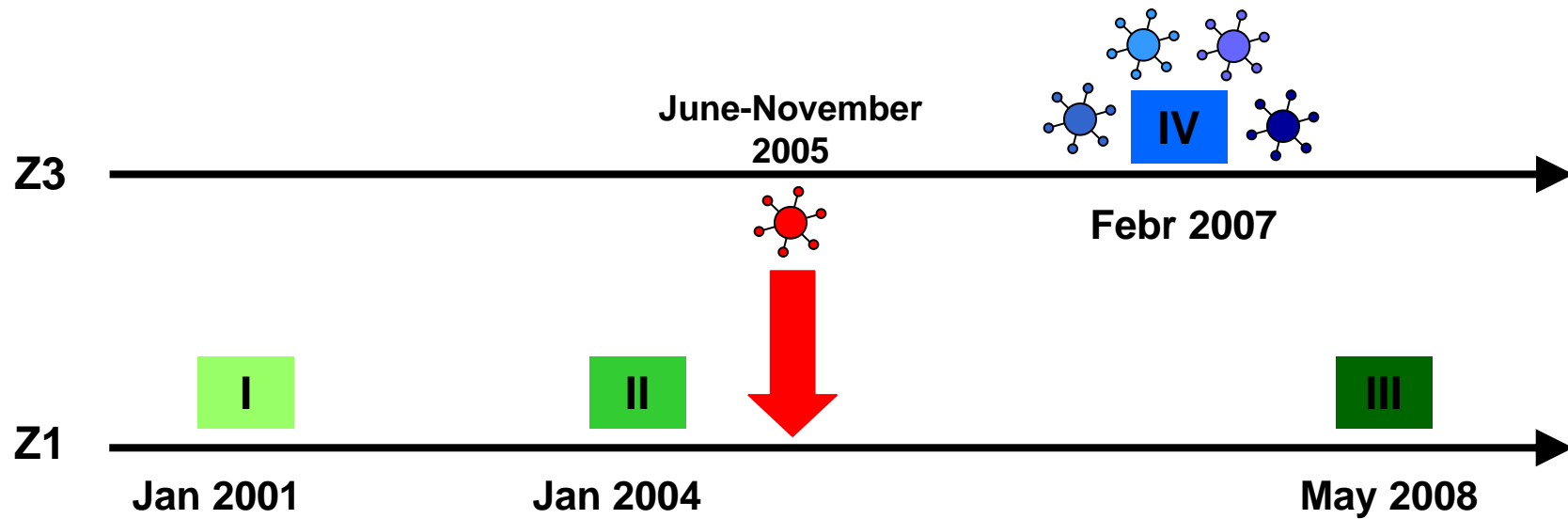
**Conclusion:**

**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?**

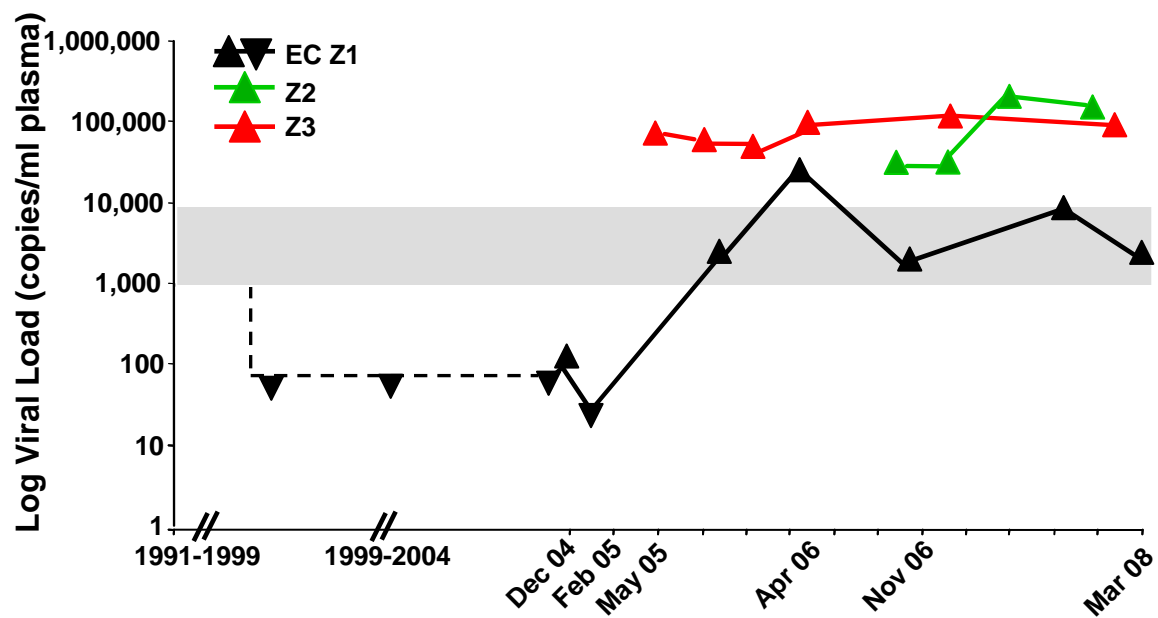
# No neutralization of Z3 virus by EC-Z1 sera





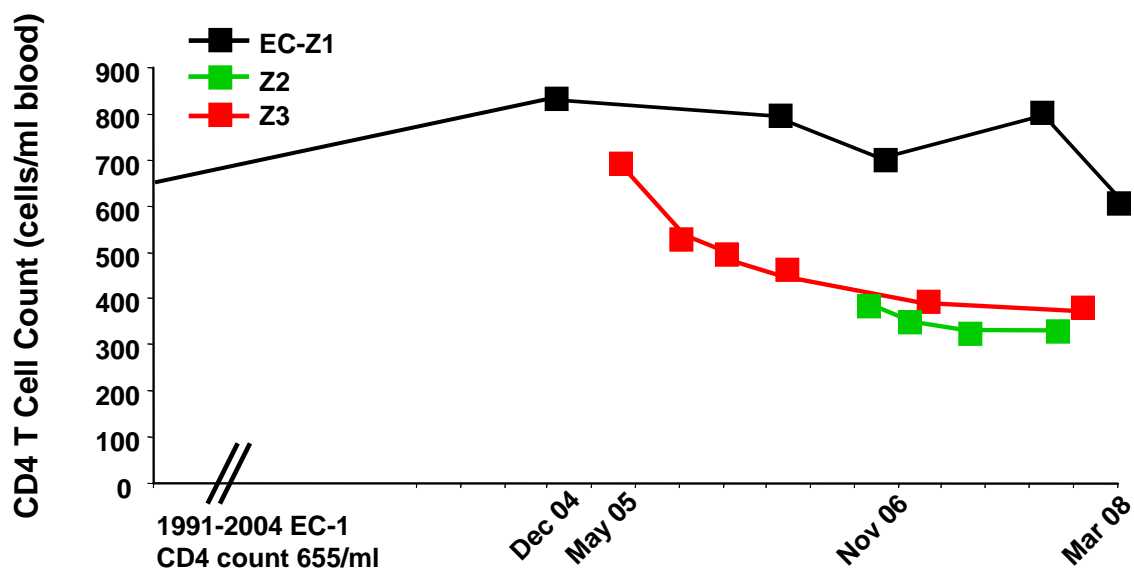
# HIV-1 load in plasma in EC-Z1 and partners

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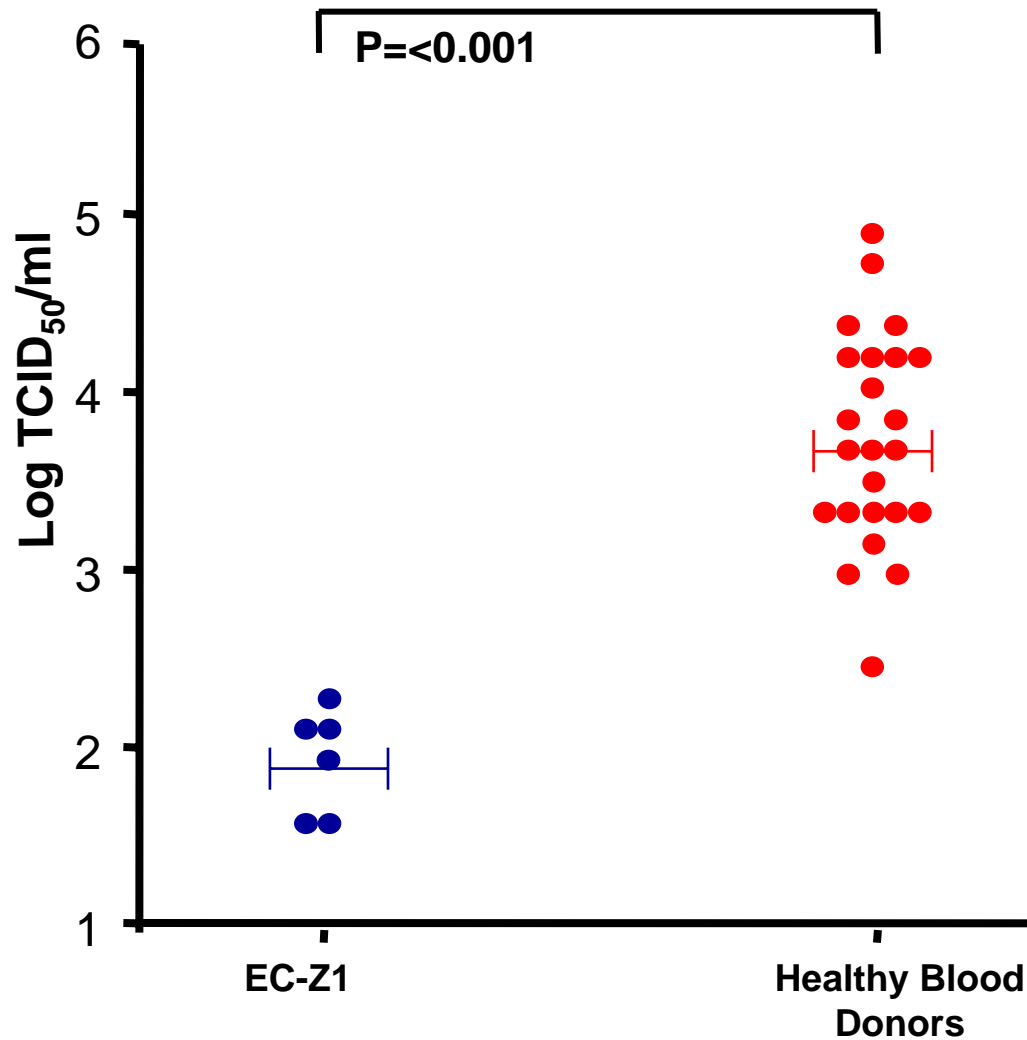
# CD4 T cell counts in EC-Z1 and partners

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

# Low HIV-1 Susceptibility of EC-Z1 PBMC

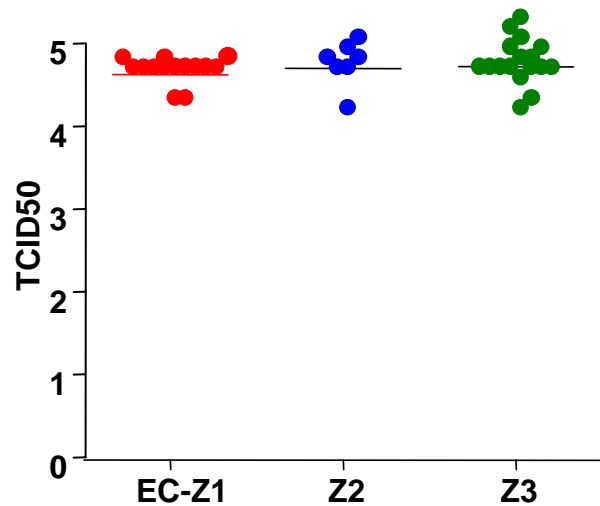


- Titration of one HIV stock on PHA stimulated PBMC from EC-Z1 (from aviremic period) and 4 healthy blood donors (6 different primary HIV variants tested (R5 and X4))

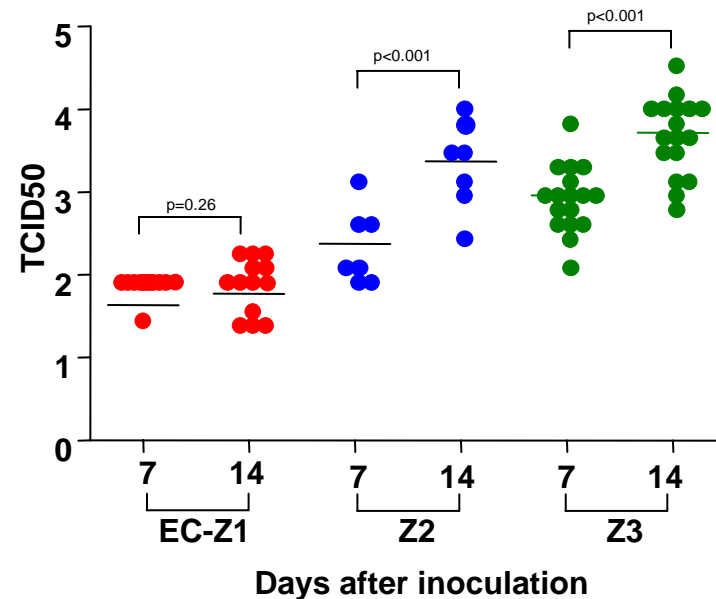
- Differences in established titre reflect differences in in-vitro HIV susceptibility

# TCID of HIV-1 variants from EC-Z1, Z2, and Z3

Titer of HIV-1 variants from EC-Z1, Z2, and Z3 on TZMbl cells



Titer of HIV-1 variants from EC-Z1, Z2, and Z3 on PBMC



- Similar titer of EC-Z1, Z2, and Z3 viruses in TZMbl cells (single round) but ~1.5 log difference on PBMC
- No spread of EC-Z1 HIV-1 in PBMC culture

# Summary

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- **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

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- **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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