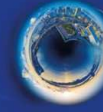


Long-term ART-free SIV Remission Following Allogeneic HSCT in Mauritian cynomolgus macaques

Helen Wu

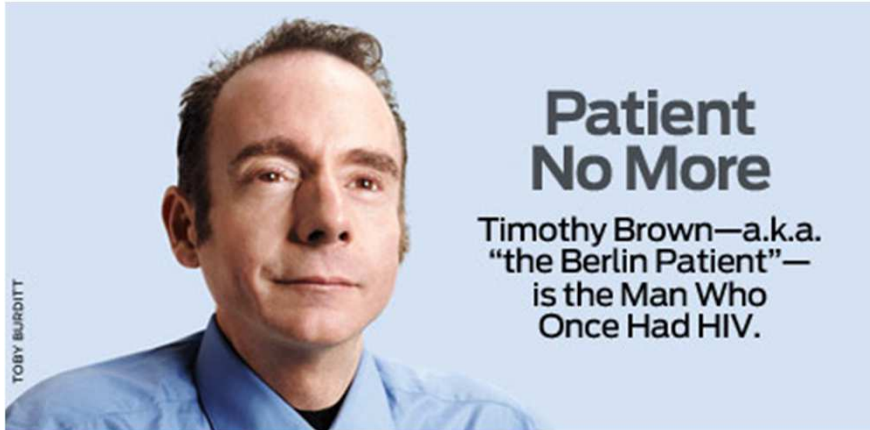
Vaccine & Gene Therapy Institute
Oregon Health & Science University



CONFLICTS OF INTEREST

No conflicts to declare

How does HSCT lead to HIV cure?



**“Berlin patient”
Timothy Brown**
HIV remission 13 years



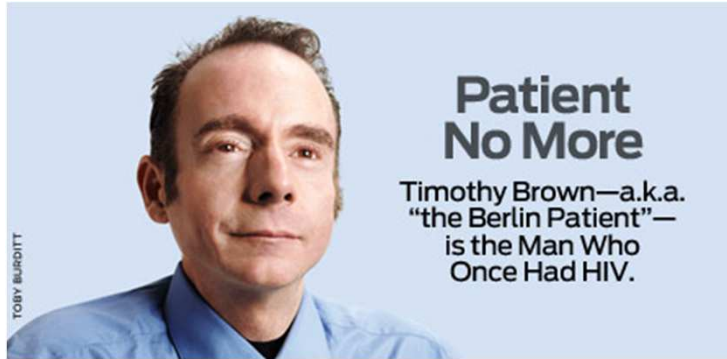
**“London patient”
Adam Castillejo**
HIV remission >5 years



IMPAACT P1107 Team Presents First Known Case of a Woman with HIV Remission

CROI 2022

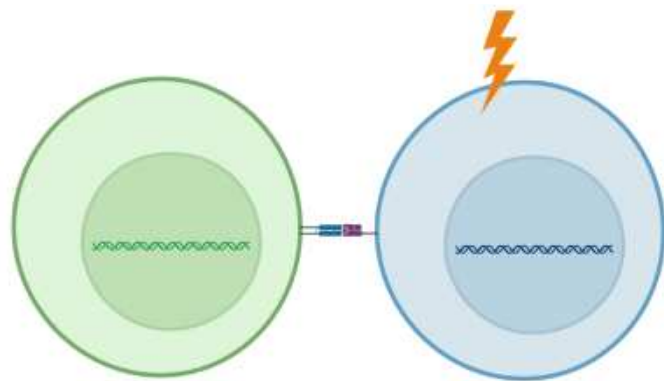
Investigating mechanism of HIV cure in Timothy Brown



- Conditioning
- **Graft-versus-host (Graft-versus-HIV) immunity**
- CCR5^{Δ32/Δ32} graft

Hypothesis: NHP model can define mechanisms of HIV cure

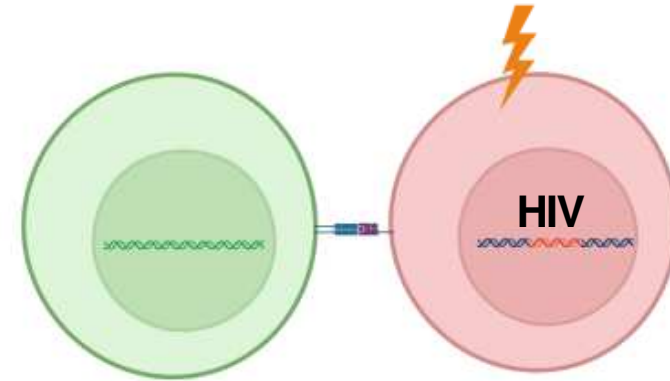
A role for graft-versus-host immunity in viral reservoir clearance



**Alloreactive
Donor cell**

**Recipient
cell**

**Allogeneic immunity
“Graft-versus-host”**



**Alloreactive
Donor cell**

**Recipient
HIV-inf.
CD4+ T cell**

**Allogeneic immunity
“Graft-versus-reservoir”**

Allogeneic HSCT (CCR5^{wt/wt}) in Mauritian cynomolgus macaques

nature communications

Allogeneic stem cell transplantation in fully MHC-matched Mauritian cynomolgus macaques recapitulates diverse human clinical outcomes

[Benjamin J. Burwitz](#), [Helen L. Wu](#), ... [Jonah B. Sacha](#)  [+ Show authors](#)



MHC-matched donor

Mobilization

G-CSF 50ug/kg x4
AMD3100 1mg/kg



Donor stem cell collection by leukapheresis

CD34 dose 3-10 x 10⁶ per kg
CD3 dose >100 x 10⁶ per kg



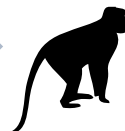
Daily combination antiretroviral therapy (TDF, FTC, DTG)

**SIV-infected
cART-suppressed recipient**



Reduced intensity conditioning
CD3-immunotoxin
Busulfan
Total body irradiation (3 Gy)

Recipient

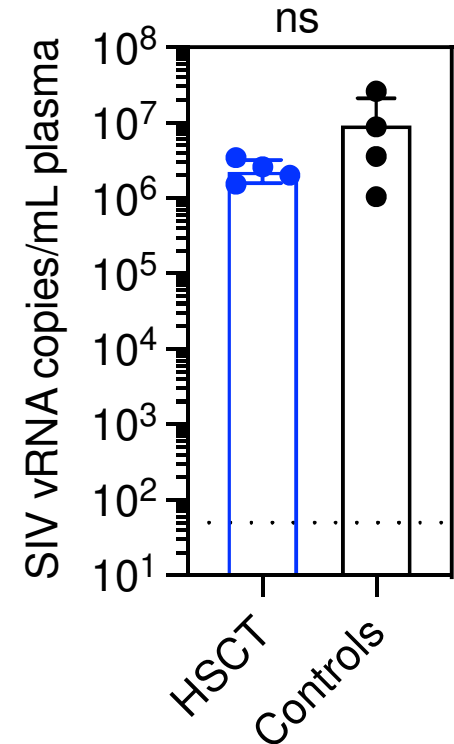
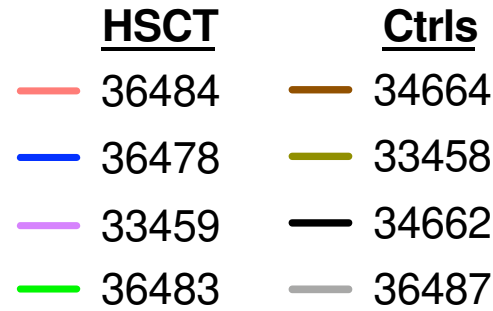
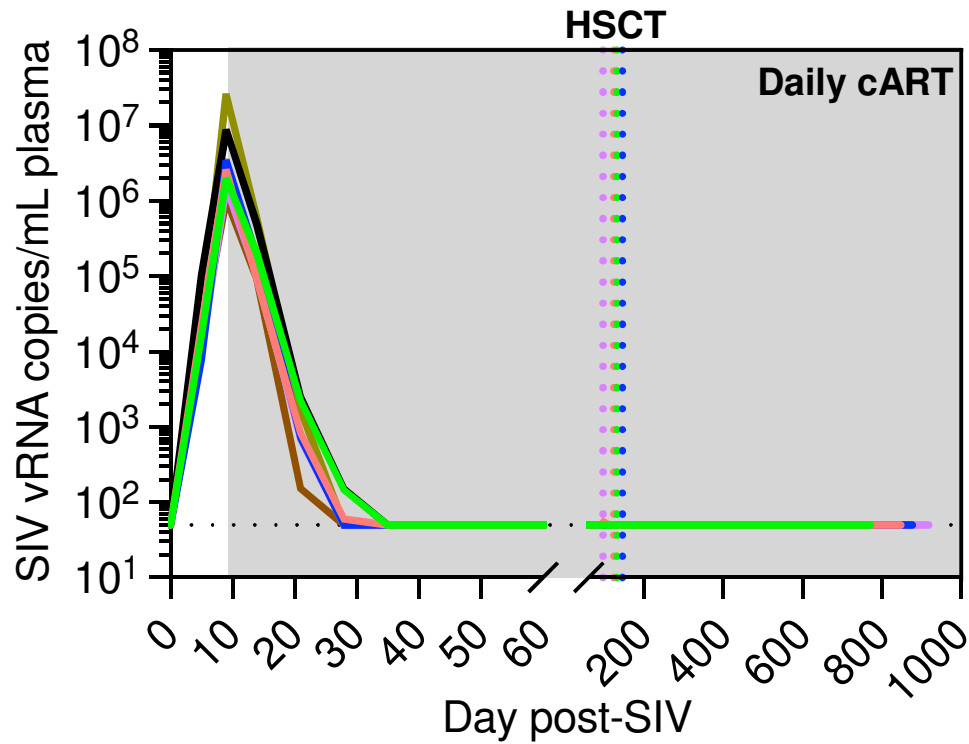


Immunosuppression/GVHD prophylaxis
Cyclophosphamide
Tacrolimus
Belatacept (CTLA4-IgG1Fc)

Discontinue
cART (ATI)

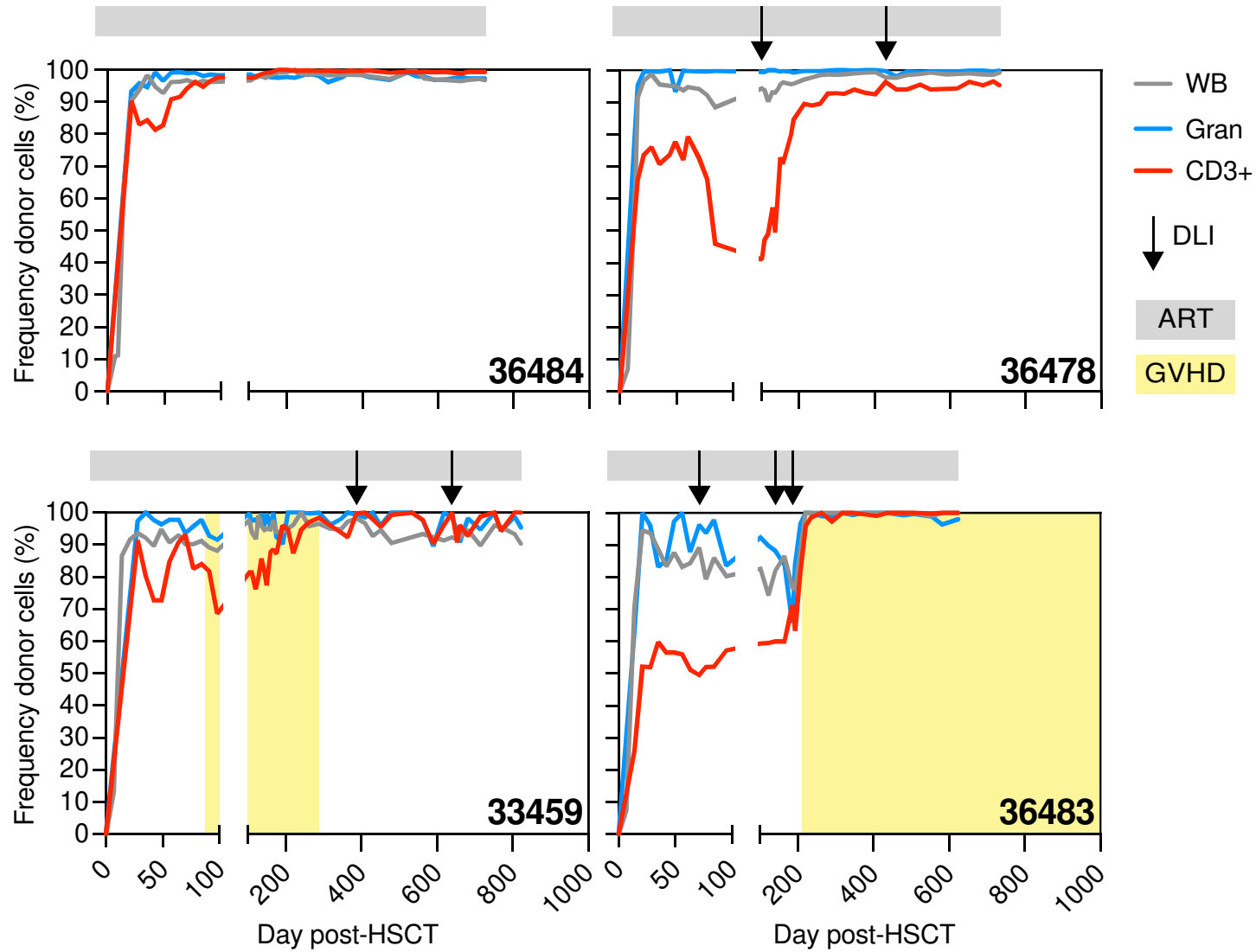


SIV plasma viral loads

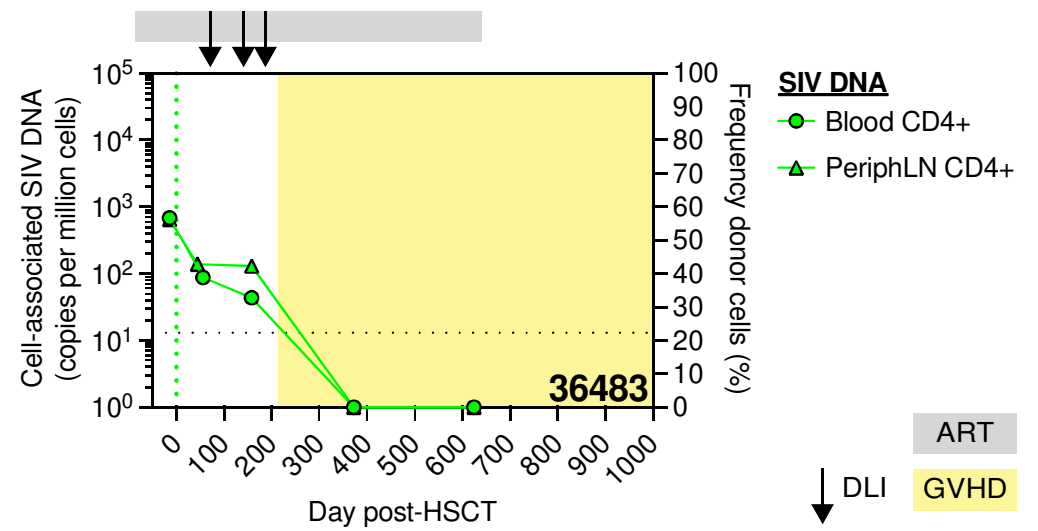


100 TCID₅₀ IV
 SIVmac239
 Daily cART (TDF, FTC, DTG) begins 9 dpi
 Daily cART admin for 12-20 weeks prior to transplant
 cART for 700-900 days total prior to release

Longitudinal donor chimerism in SIV+ HSCT recipients



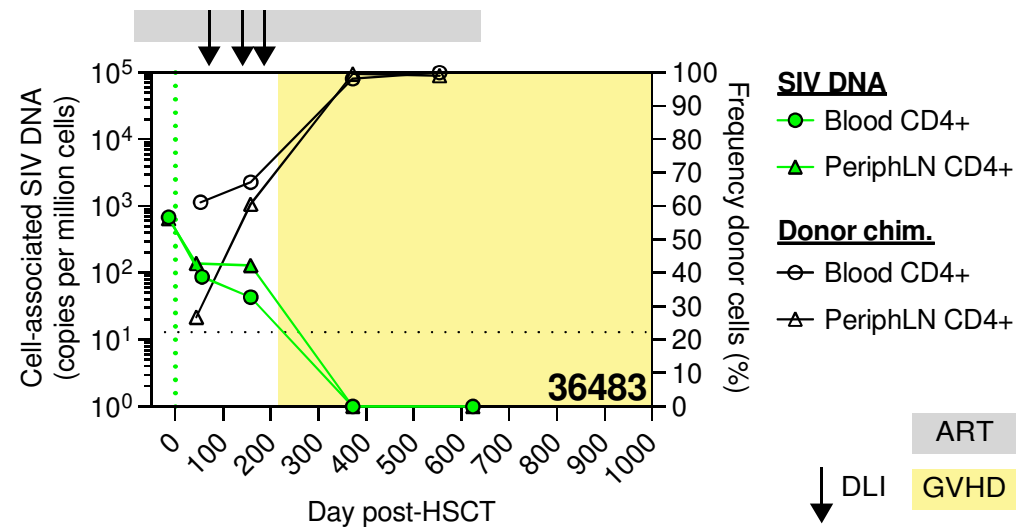
Longitudinal CD4+ cell-associated SIV DNA



cART period

Undetectable graphed as 1

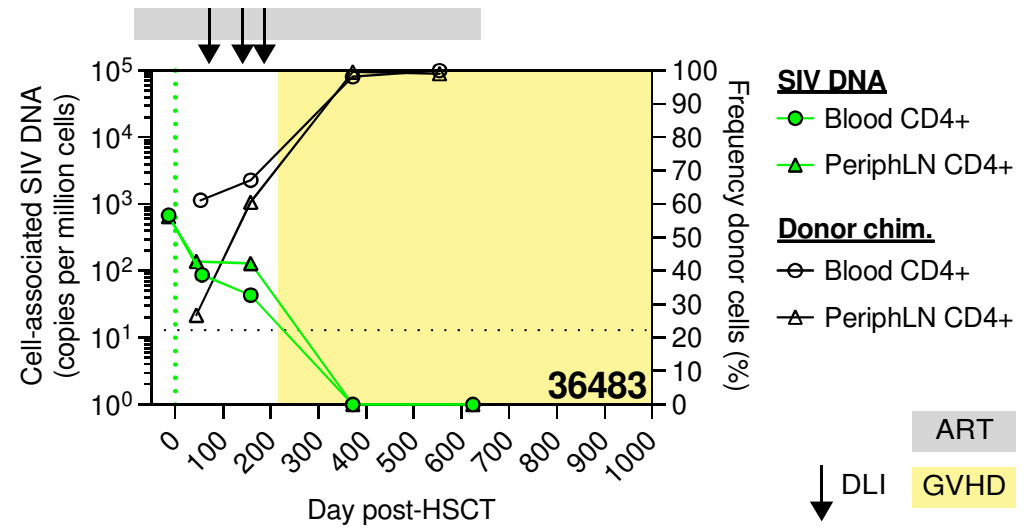
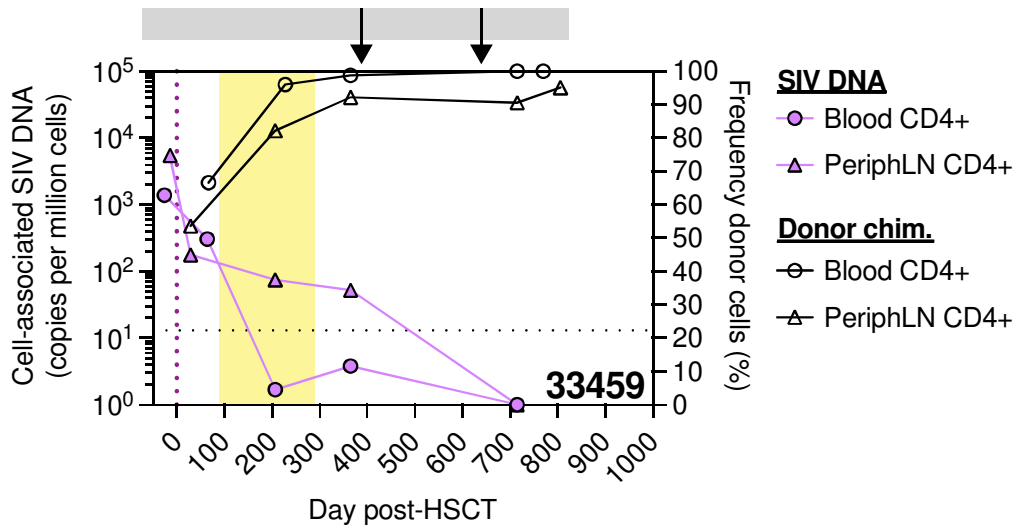
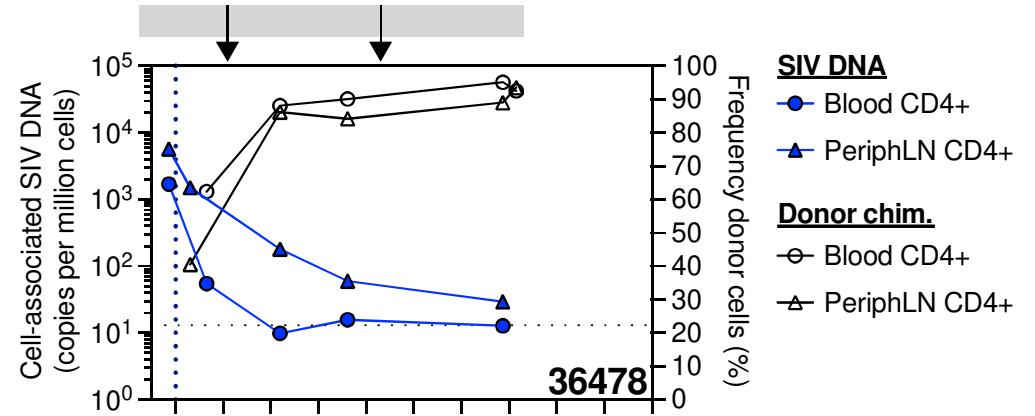
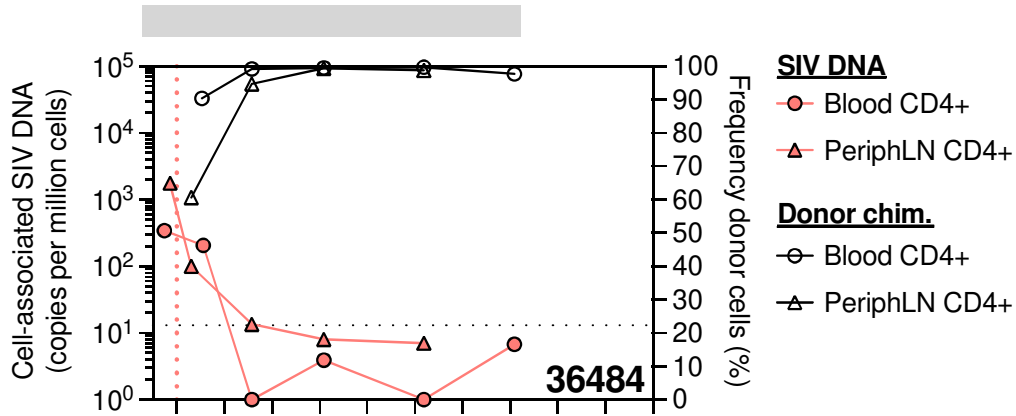
Longitudinal CD4+ cell-associated SIV DNA



cART period

Undetectable graphed as 1

Longitudinal CD4+ cell-associated SIV DNA

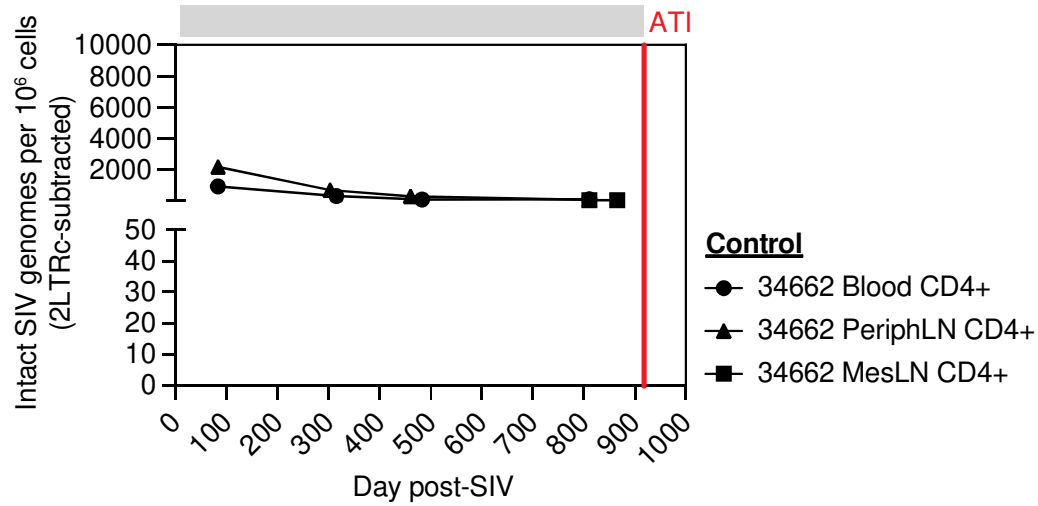


ART
 ↓ DLI
 GVHD

cART period

Undetectable graphed as 1

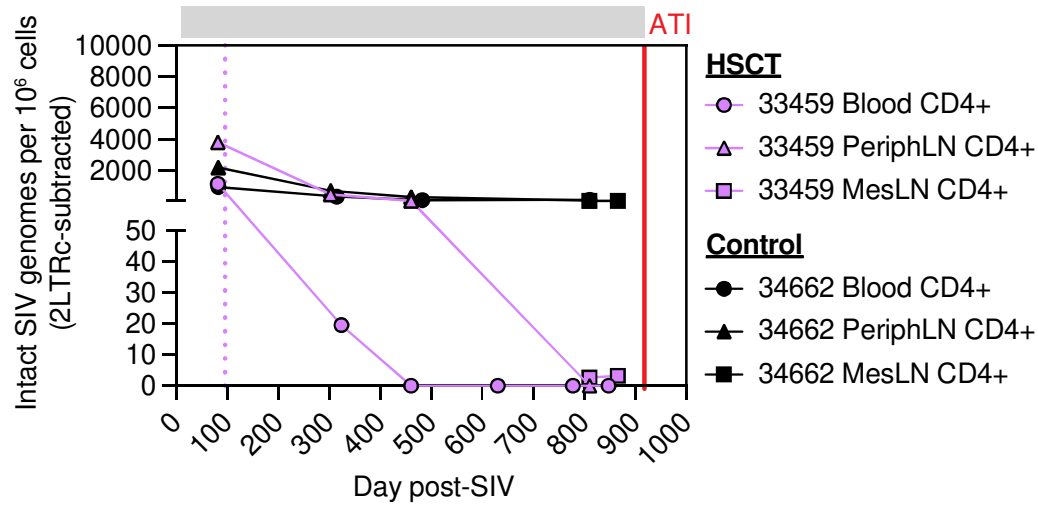
Longitudinal intact proviral DNA in HSCT recipients versus controls



cART period

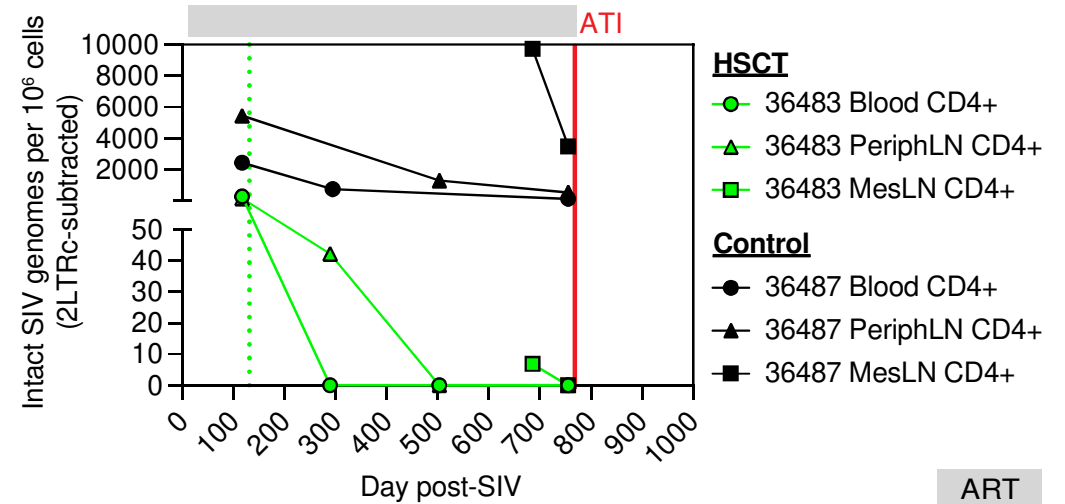
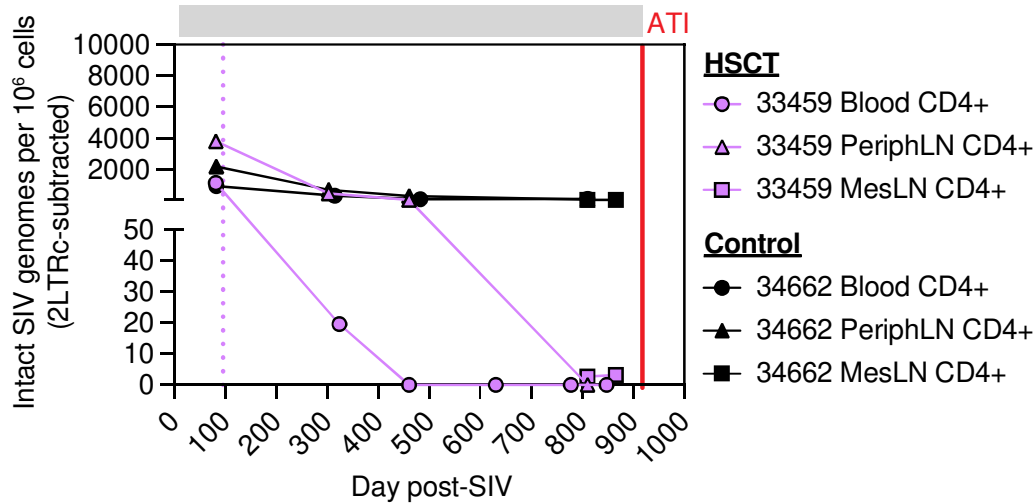
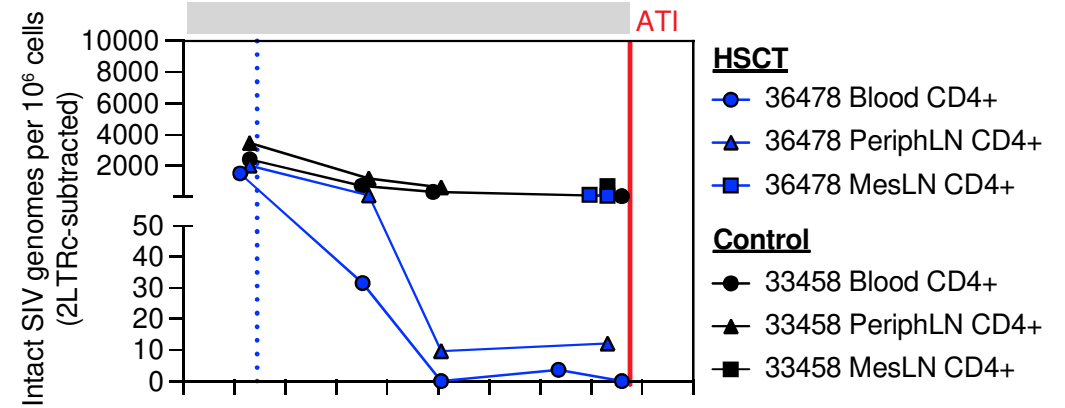
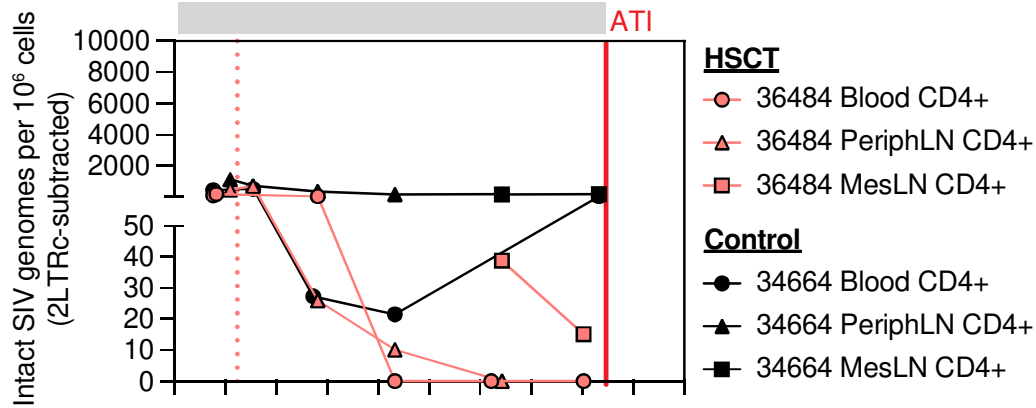
Siliciano Lab

Longitudinal intact proviral DNA in HSCT recipients versus controls



cART period

Longitudinal intact proviral DNA in HSCT recipients versus controls



ART

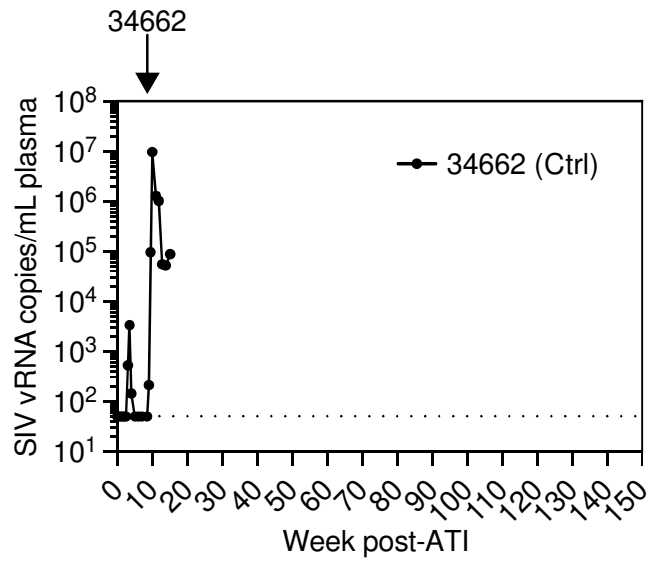
cART period

Siliciano Lab

Analytical treatment interruption (ATI)

ATI period

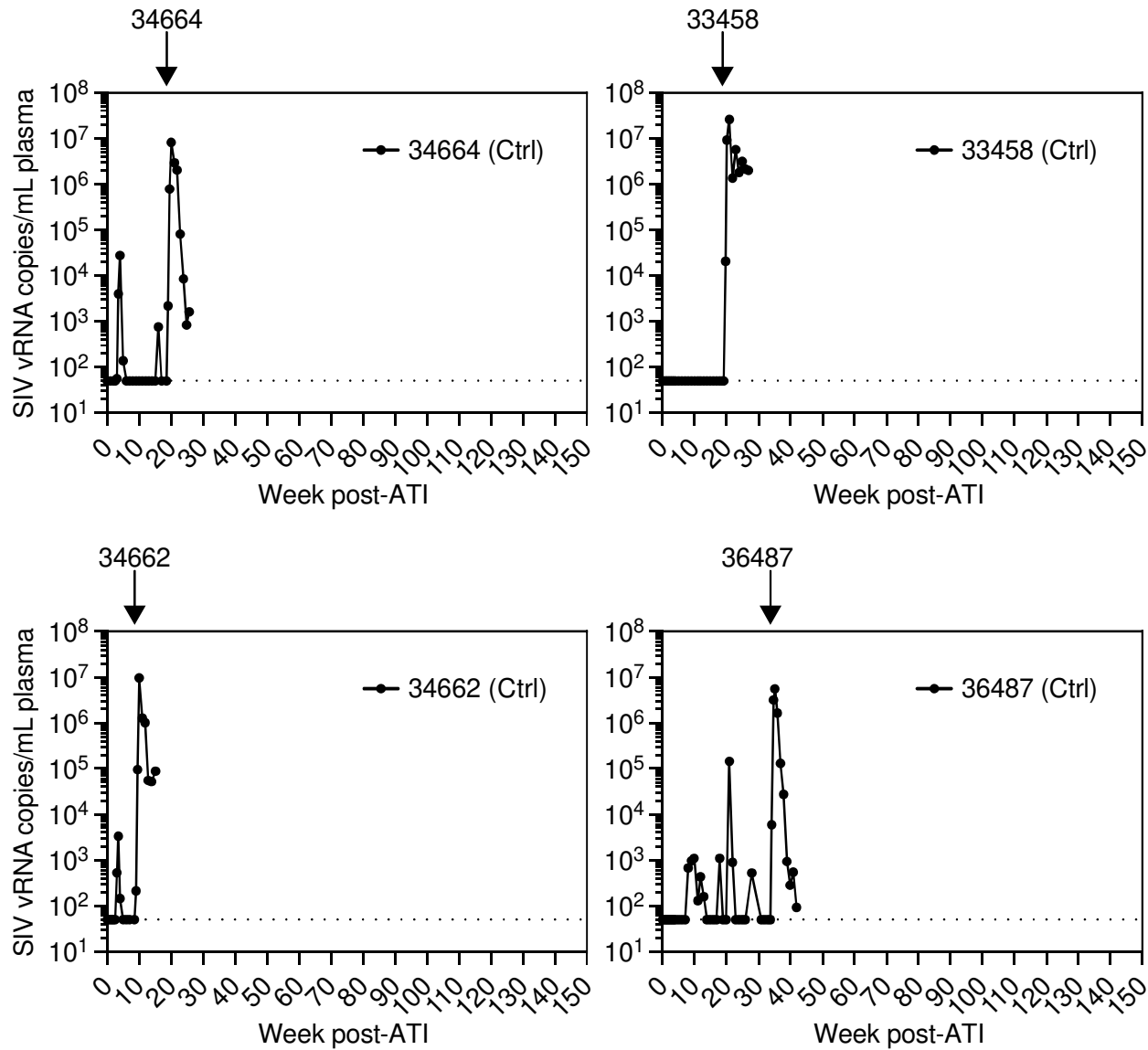
↓ CD8α depl.
↓ (first dose)



Analytical treatment interruption (ATI)

ATI period

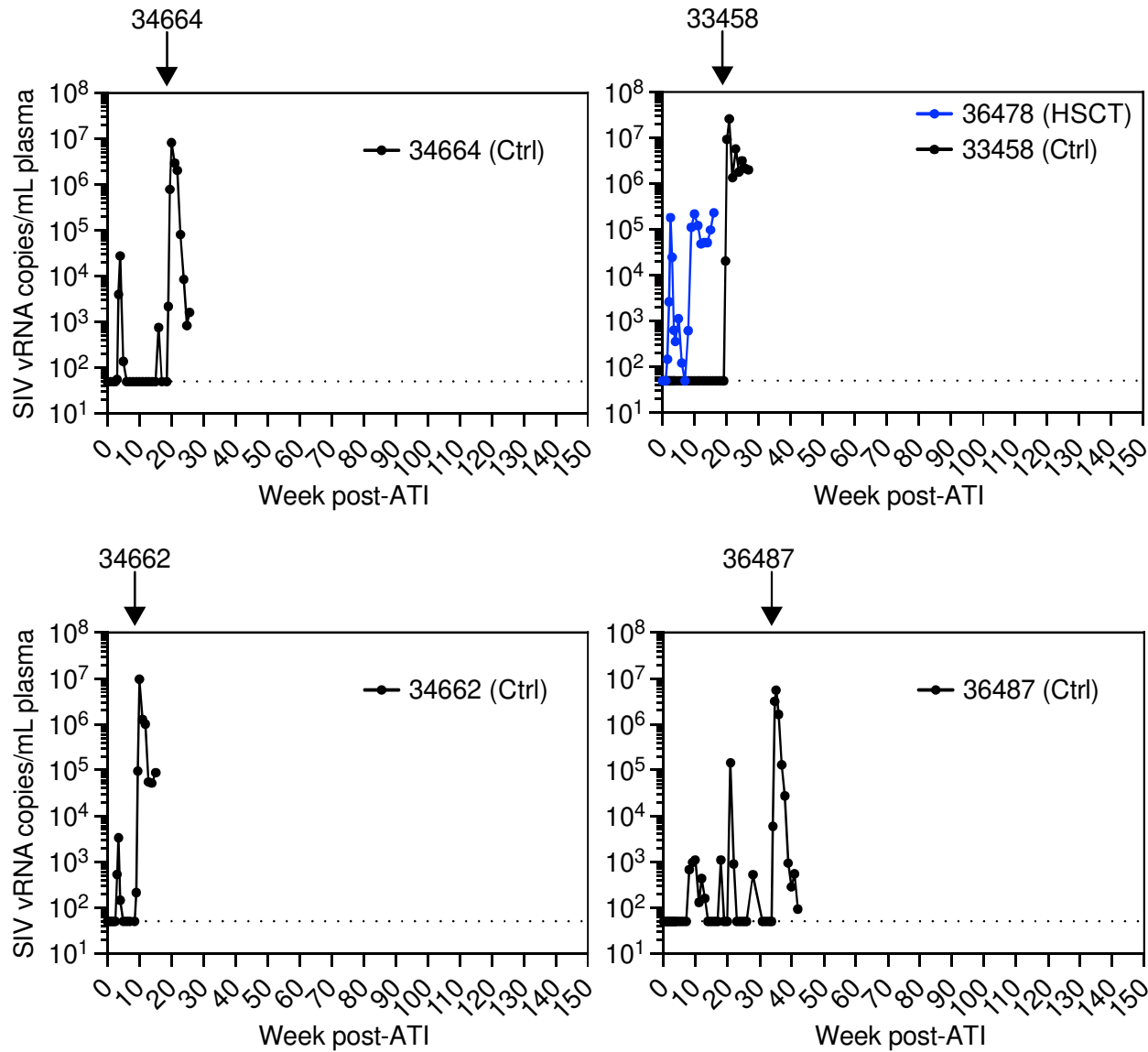
↓ CD8α depl.
(first dose)



Analytical treatment interruption (ATI)

ATI period

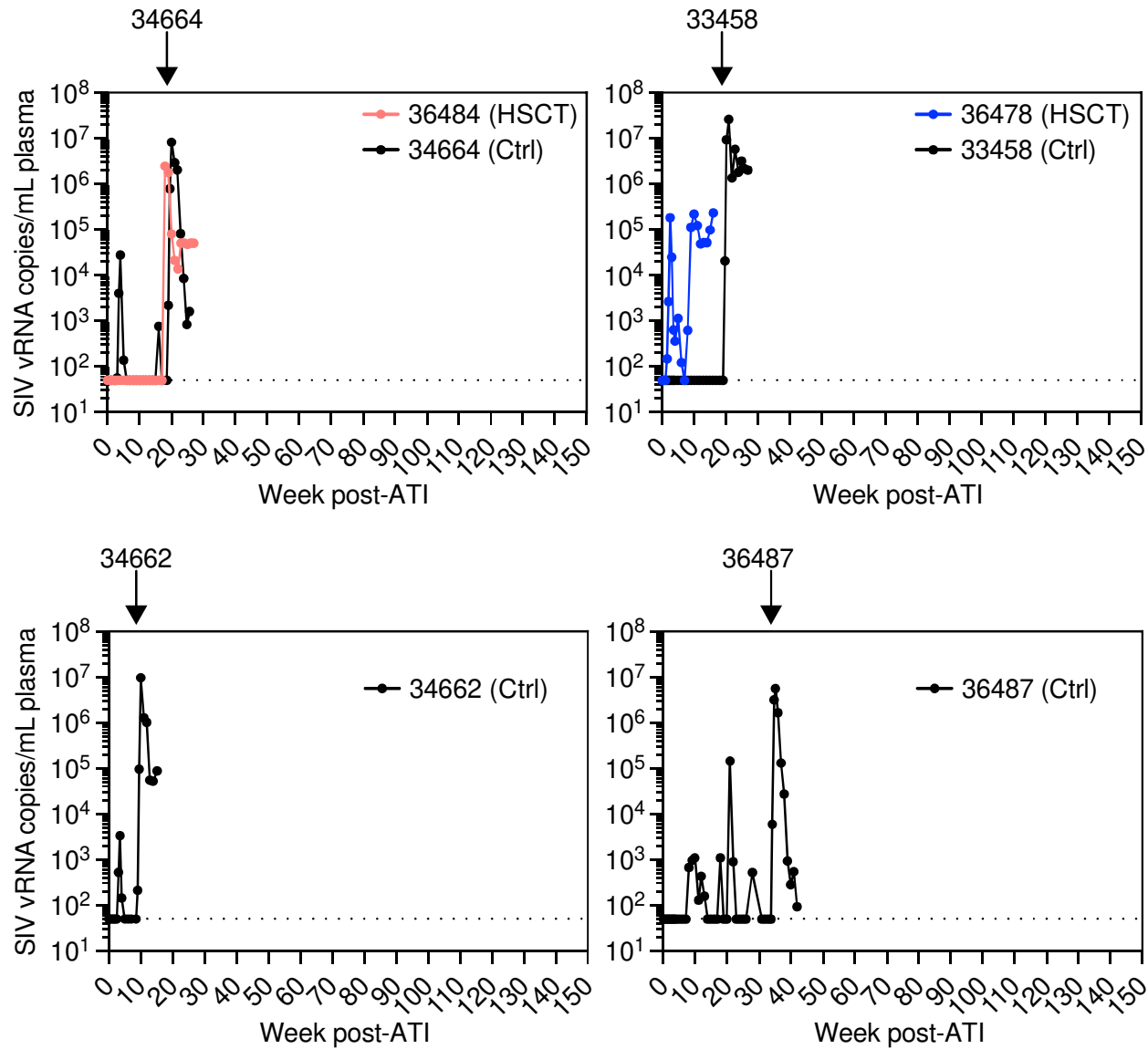
↓ CD8α depl.
(first dose)



Analytical treatment interruption (ATI)

ATI period

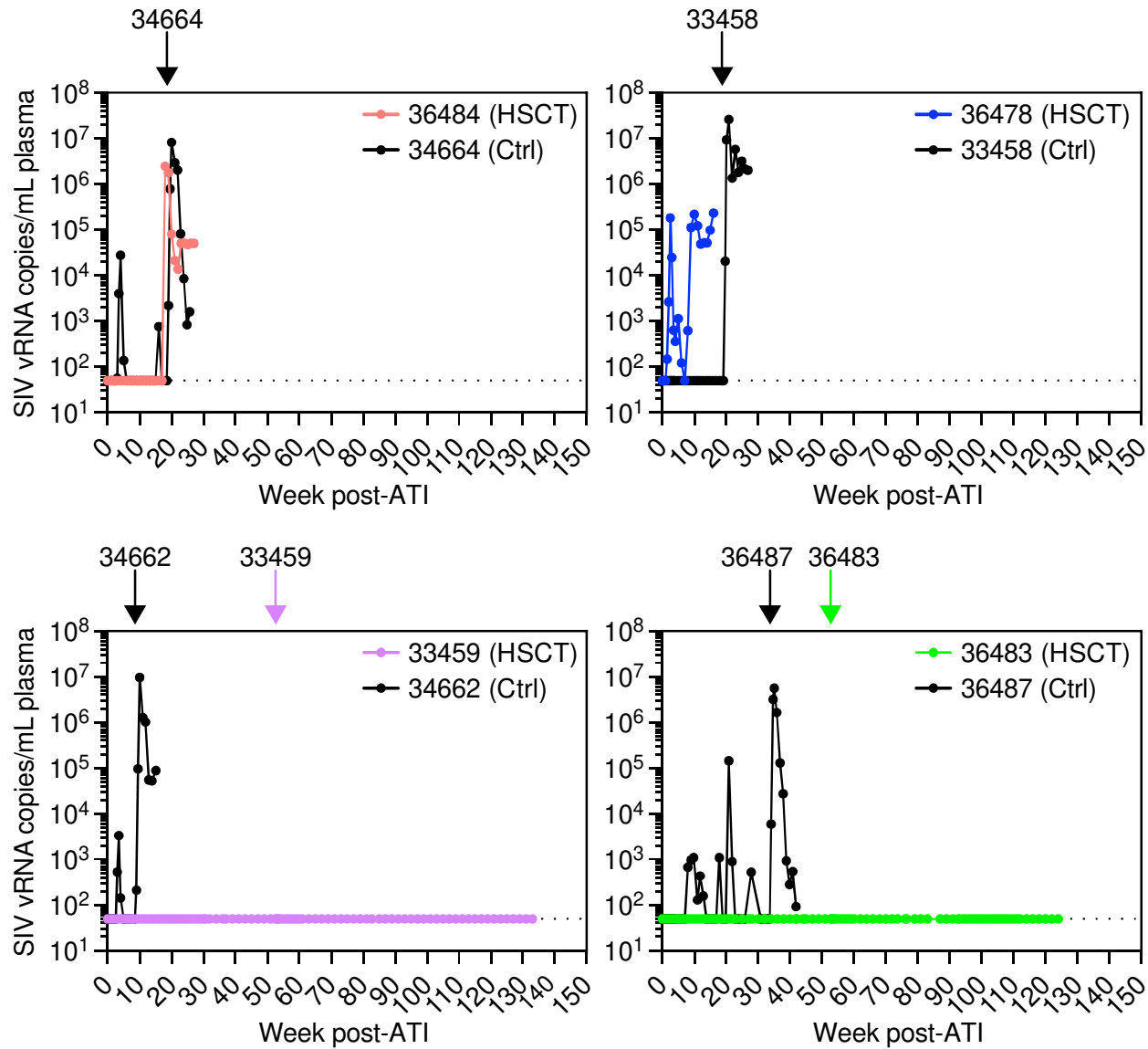
↓ CD8α depl.
(first dose)



Analytical treatment interruption (ATI)

ATI period

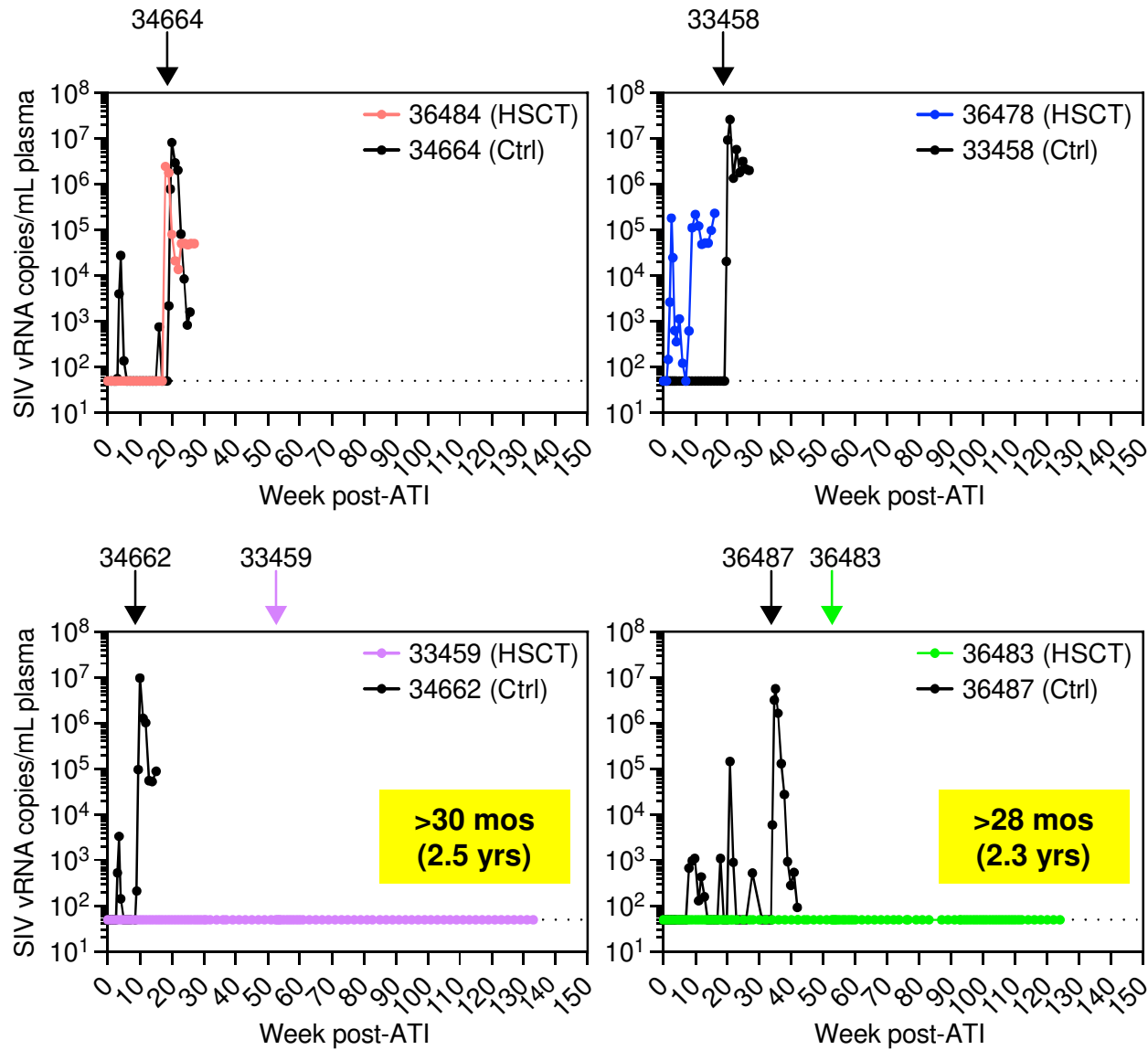
↓ CD8α depl.
(first dose)



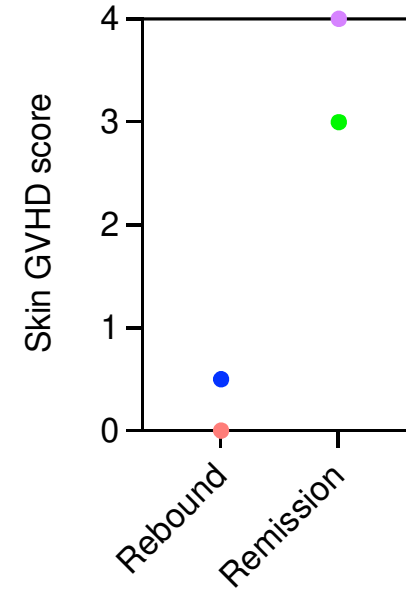
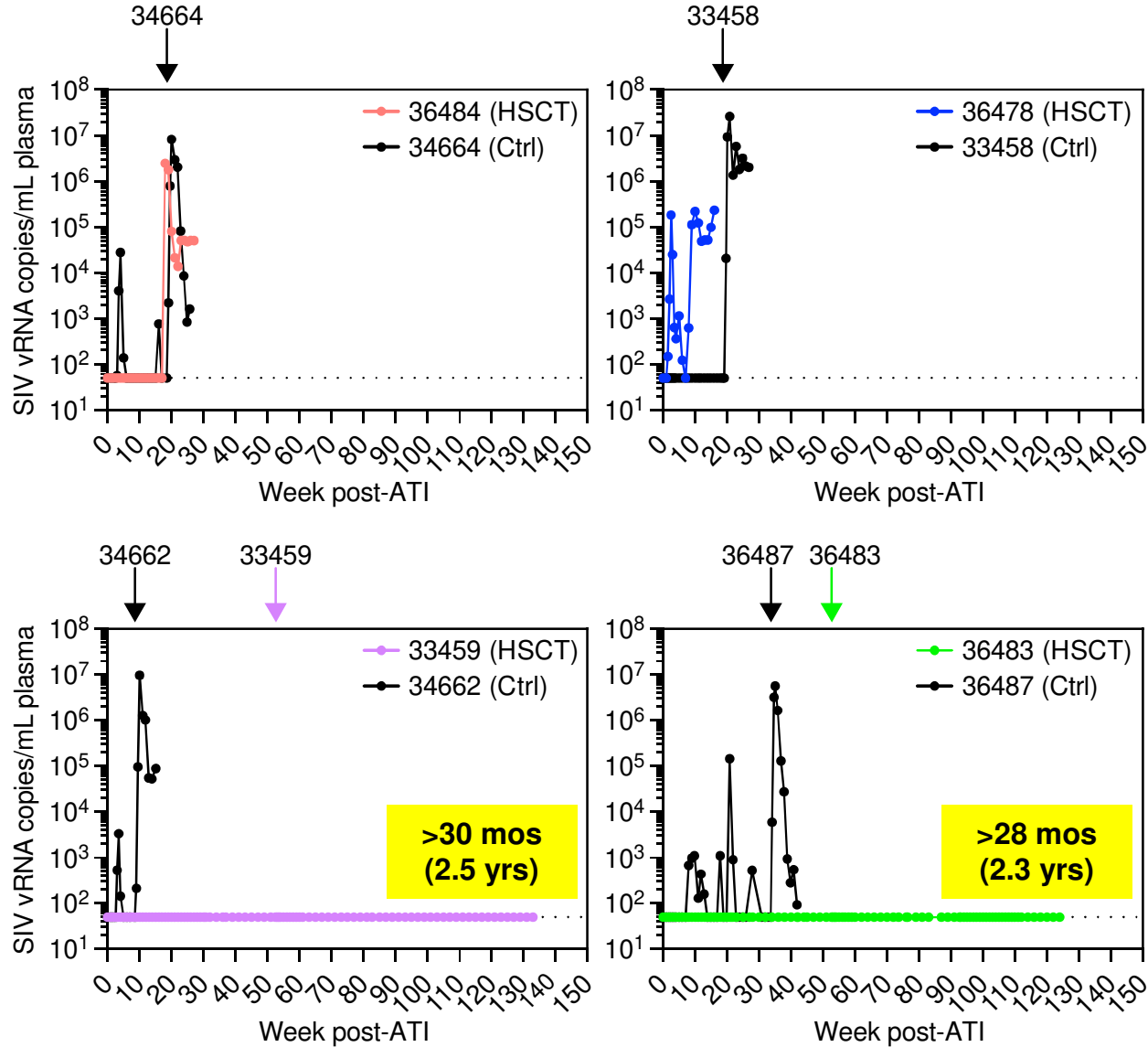
Analytical treatment interruption (ATI)

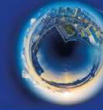
ATI period

↓ CD8α depl.
(first dose)



Allogeneic HSCT outcomes





COMMUNITY SUMMARY

- **Key question:** How does alloHSCT mediate HIV cure?
- **Key finding:** Allogeneic immunity (donor vs. recipient) drives clearance of immunodeficiency virus reservoirs through elimination of recipient CD4+ T cells.
- **Next steps:**
 - Can allogeneic immunity be safely harnessed for curative approaches, without alloHSCT?
 - Modeling CCR5d32/d32 alloHSCT using antibody-mediated CCR5 blockade

Acknowledgements

VGTI

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Mortari

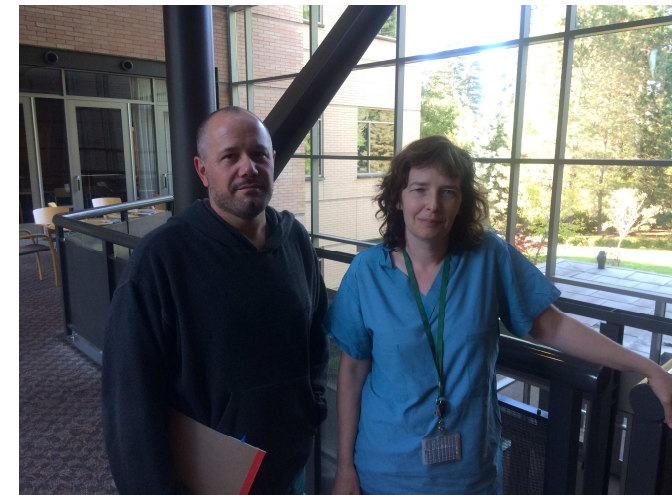
Funding sources

National Institutes of Health
R21 AI112433
R01 AI129703

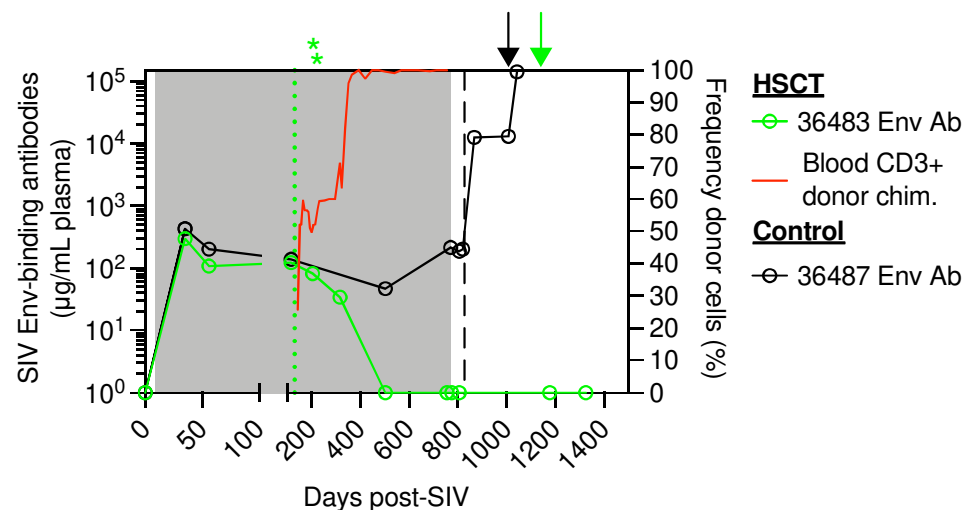
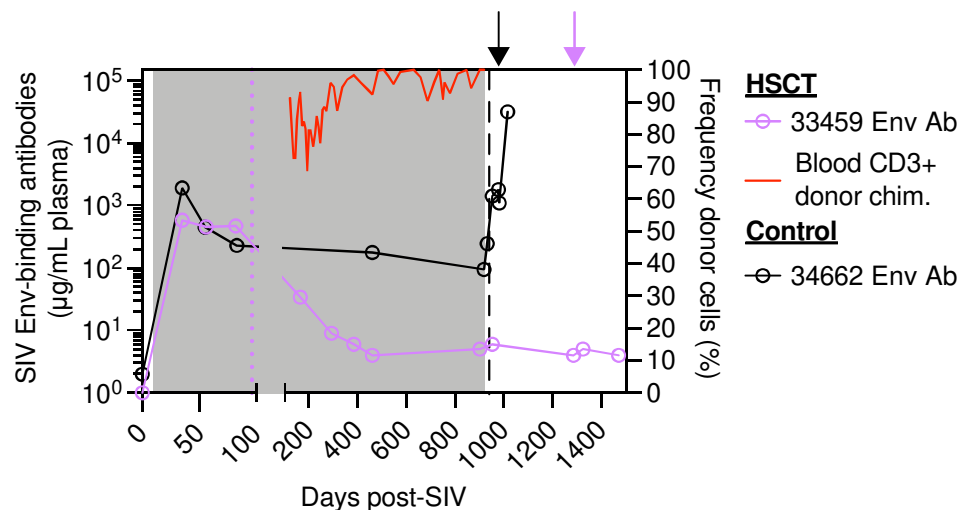
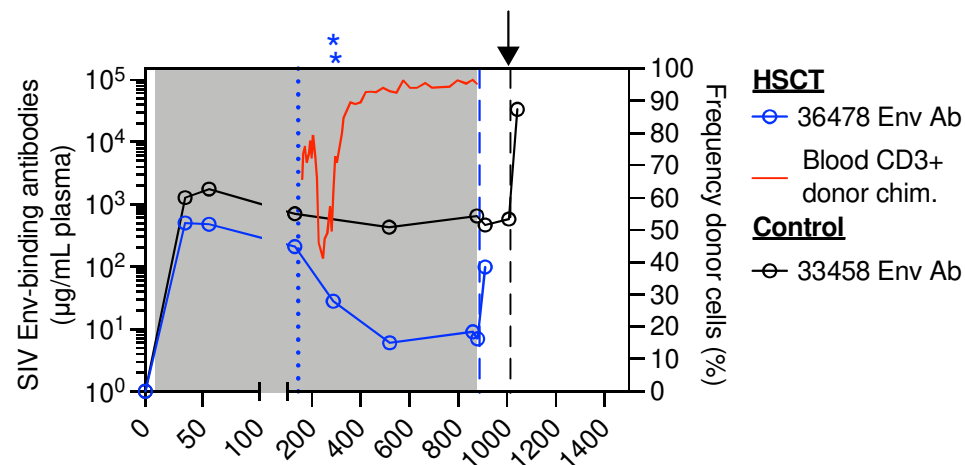
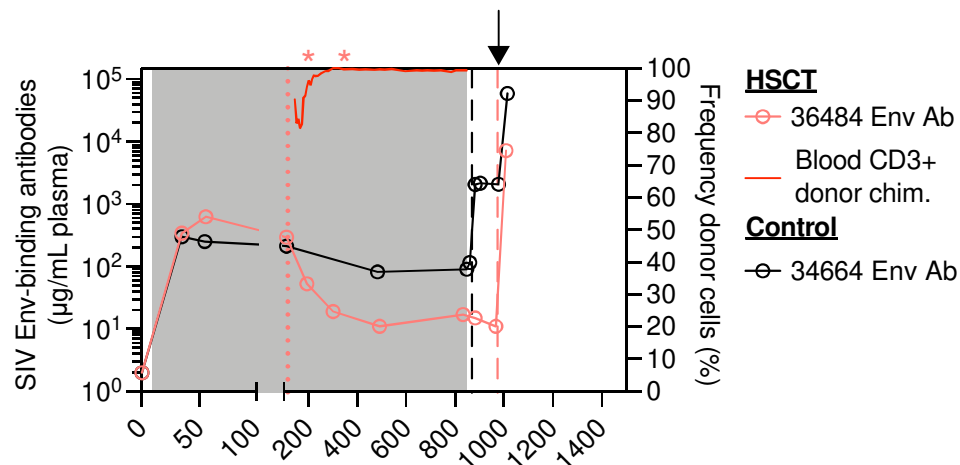
American Foundation
for AIDS Research
Grant 108832-55-RGRL

Johns Hopkins

Bob Siliciano
Janet Siliciano
Mithra Kumar
Emily Fray

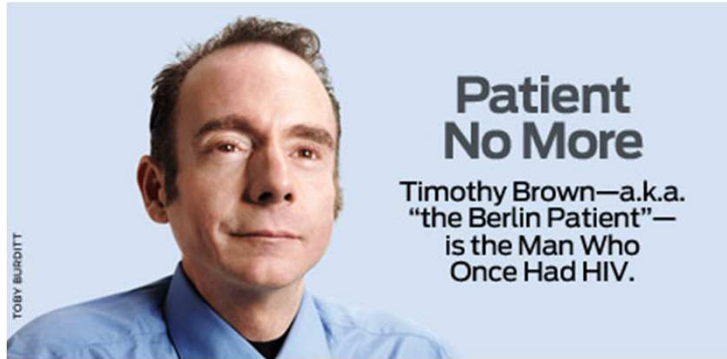


SIV Env-binding antibody titers



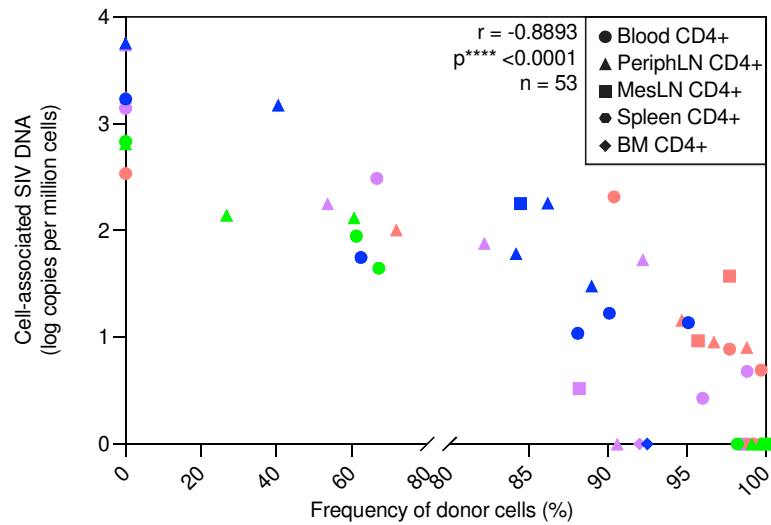
..... HSCT | First detectable SIV pVL * anti-CD20 ↓ CD8α depl. (first dose)

How does HSCT lead to HIV cure?

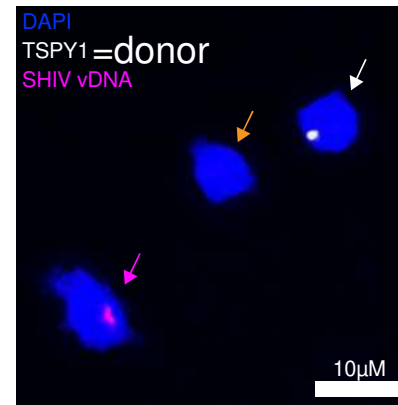


- Conditioning
- Graft-versus-host (Graft-versus-HIV) immunity
- CCR5 Δ 32/ Δ 32 graft

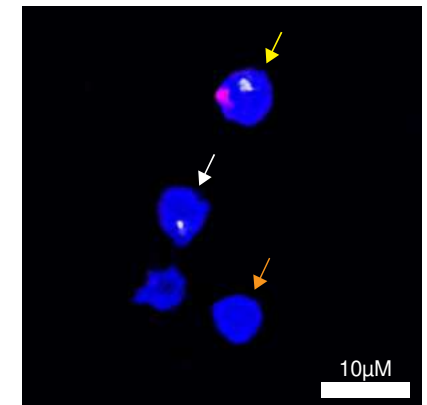
Alloimmunity clears latent virus



CCR5 deficiency shields donor cells



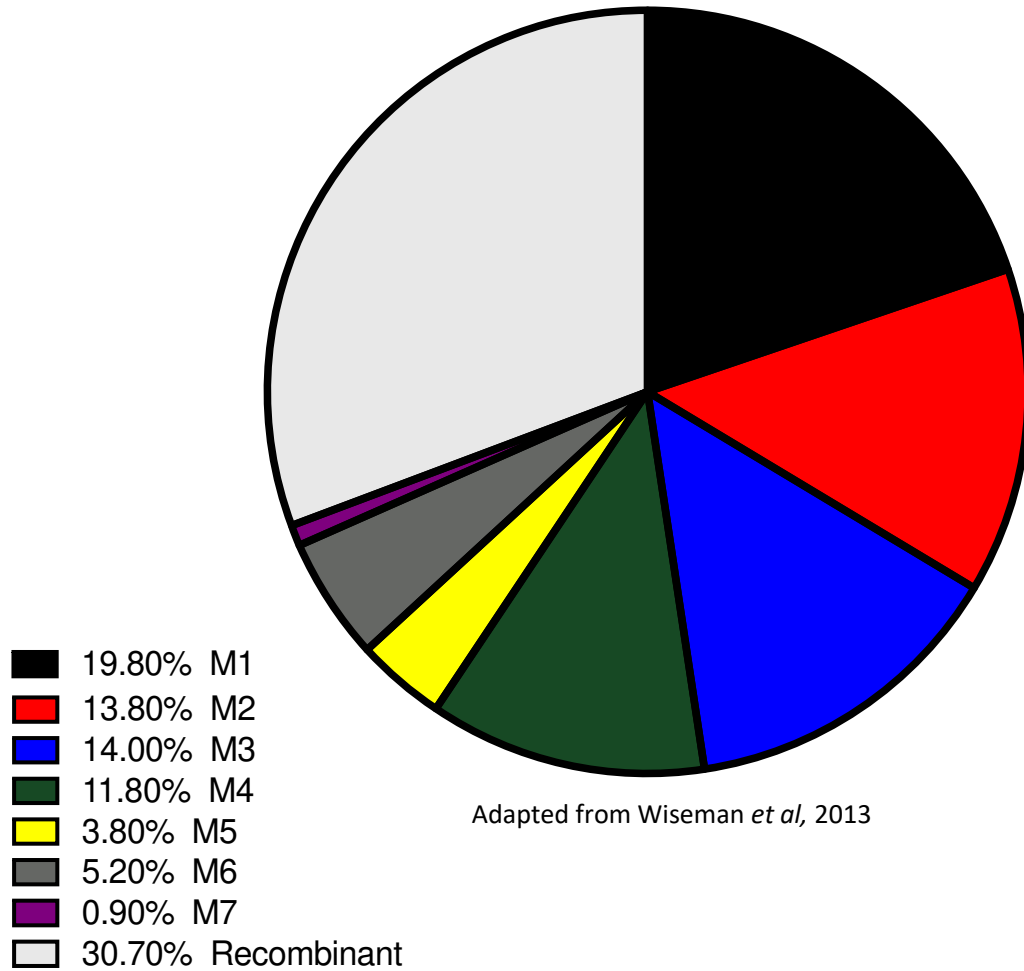
PeriphLN CD4+
d51 post-HSCT



Estes lab

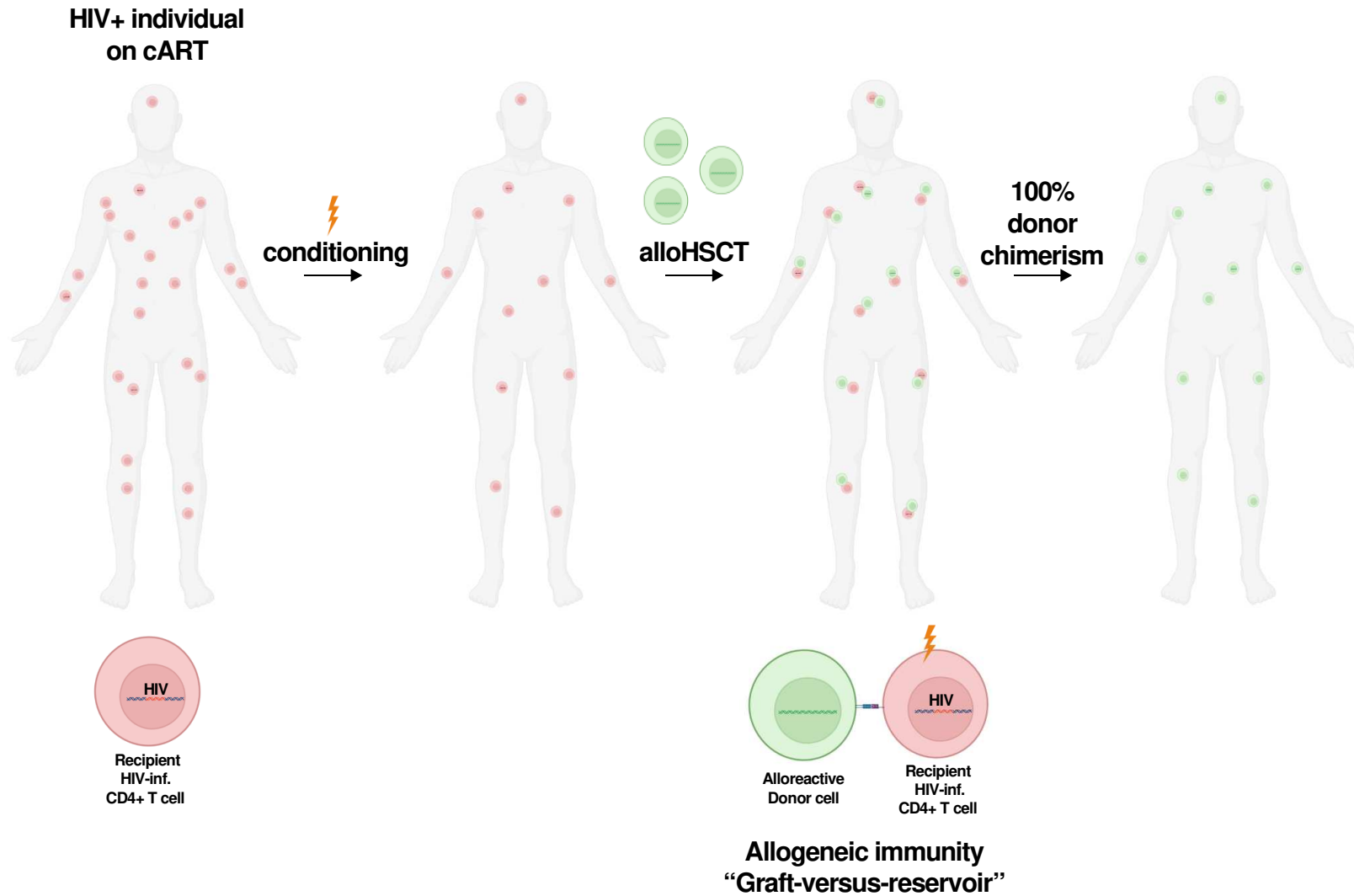
Fully MHC-matched allogeneic HSCT with Mauritian cynomolgus macaques

Frequencies of MHC haplotypes in MCM population

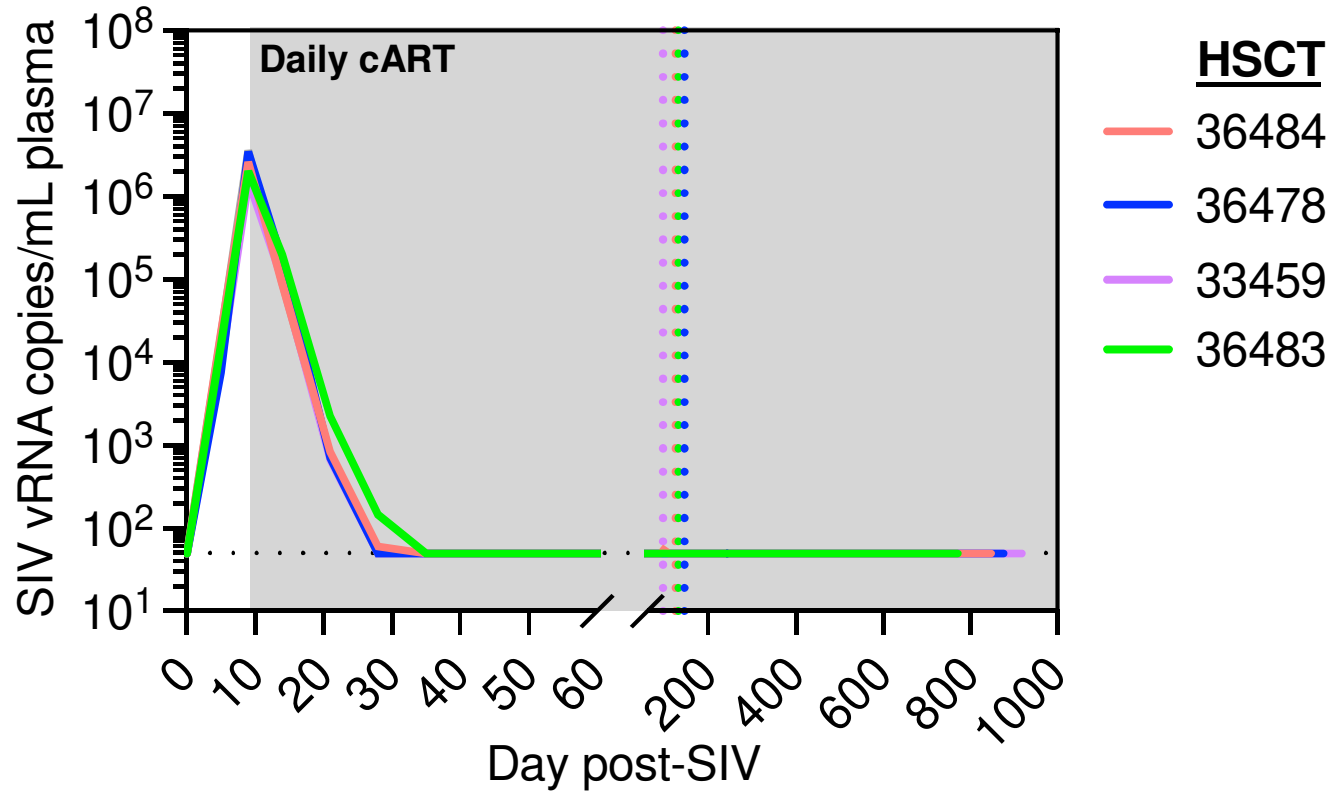


	Haplotype 1	Haplotype 2
Donor 1	M2	M4
Recipient 1	M2	M4
Donor 1	M2	M6
Recipient 1	M2	M6
Donor 1	M3	M3
Recipient 1	M3	M3
Recipient 2	M3	M3
Donor 1	M1	M1
Recipient 1	M1	M1
Recipient 2	M1	M1
Recipient 3	M1	M1

Graft-versus-host immunity

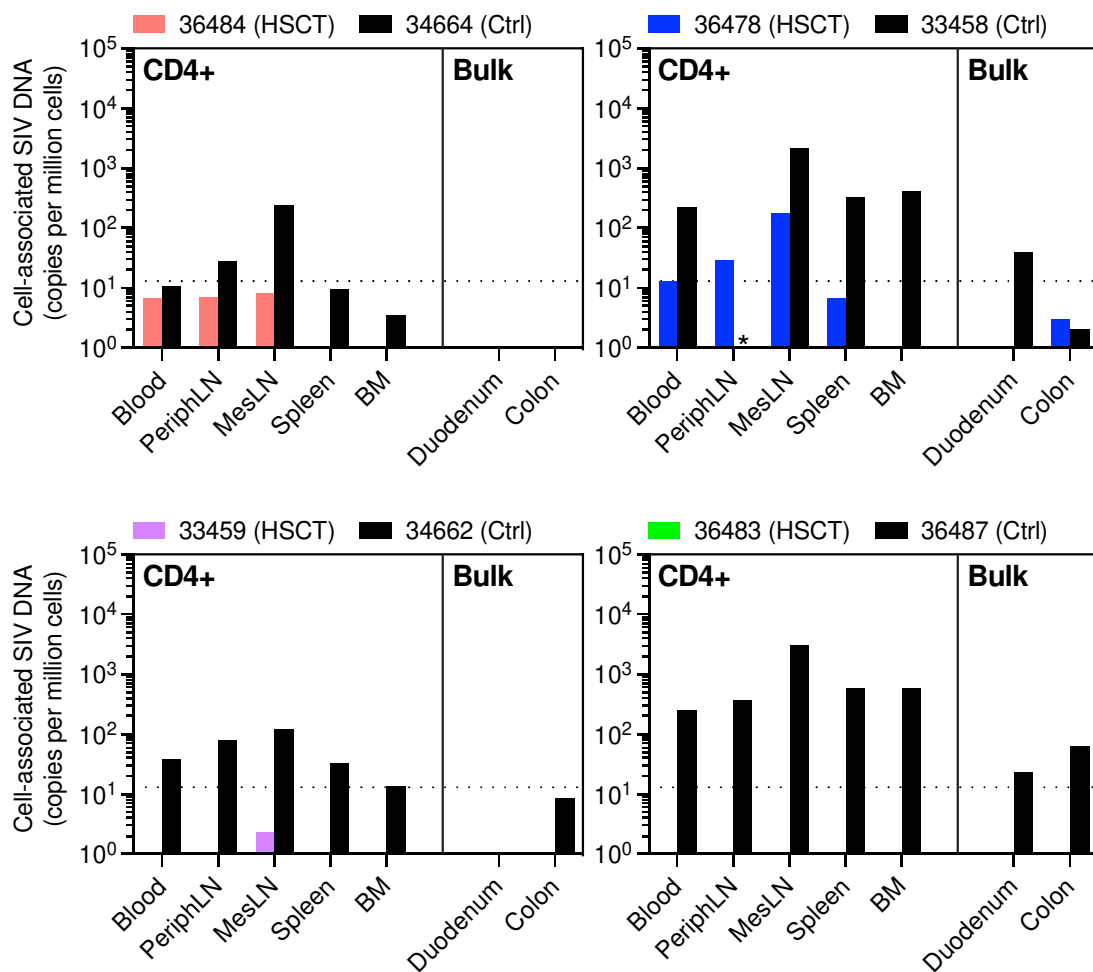


SIV plasma viral loads in HSCT recipients



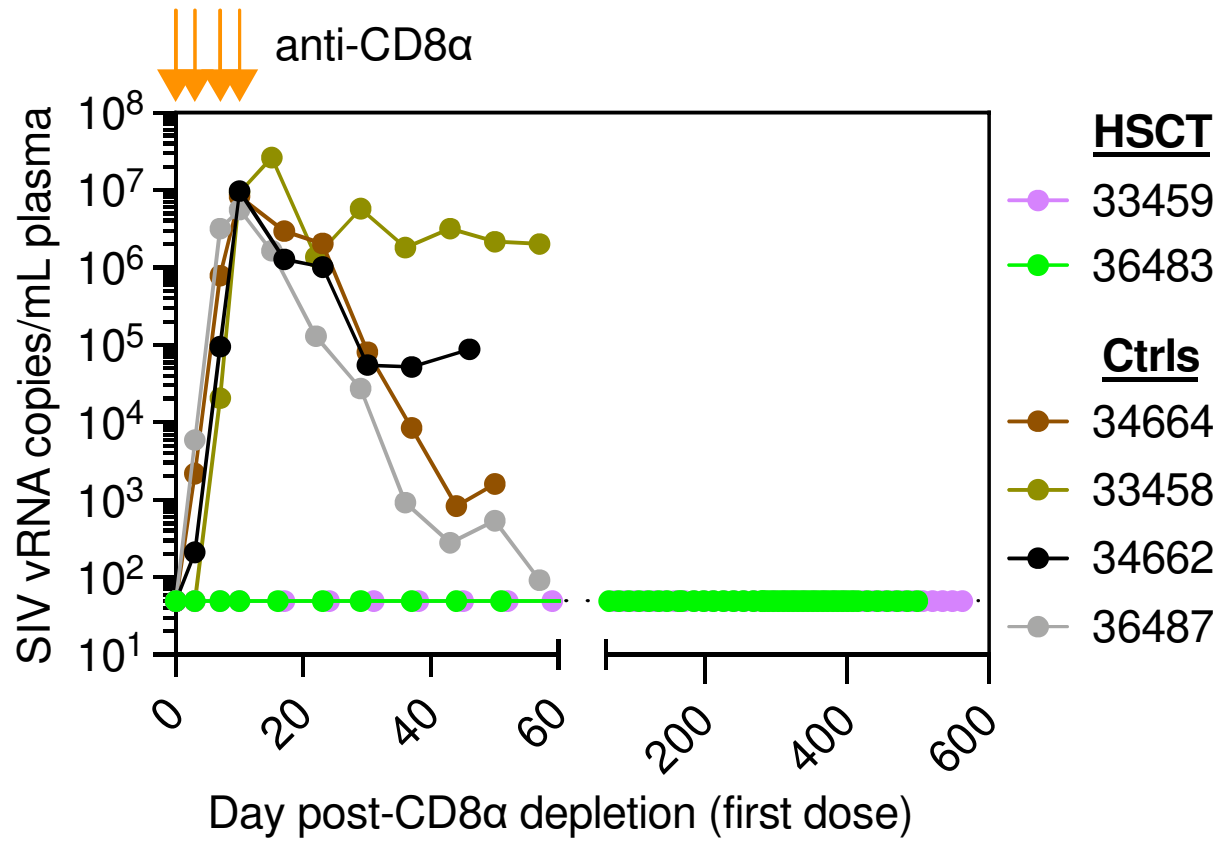
100 TCID₅₀ IV
SIVmac239
Daily cART (TDF, FTC, DTG) begins 9 dpi
Daily cART admin for 12-20 weeks prior to transplant
cART for 700-900 days total prior to release

Pre-ATI SIV DNA levels

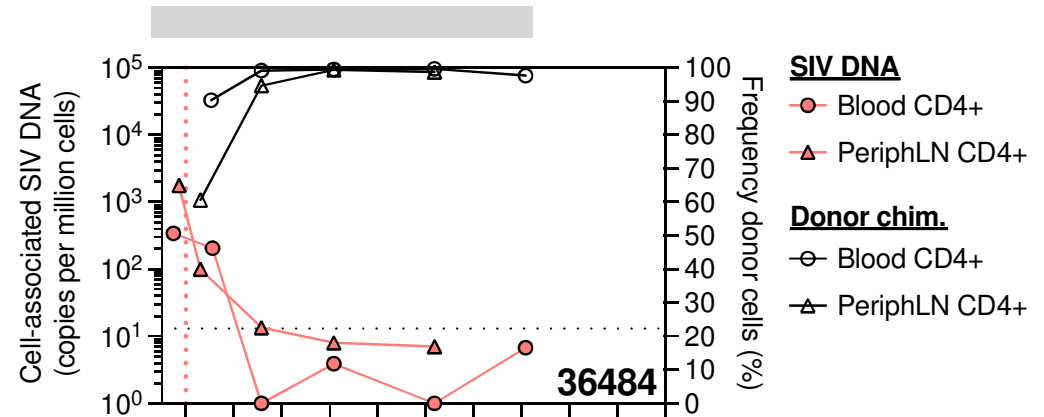
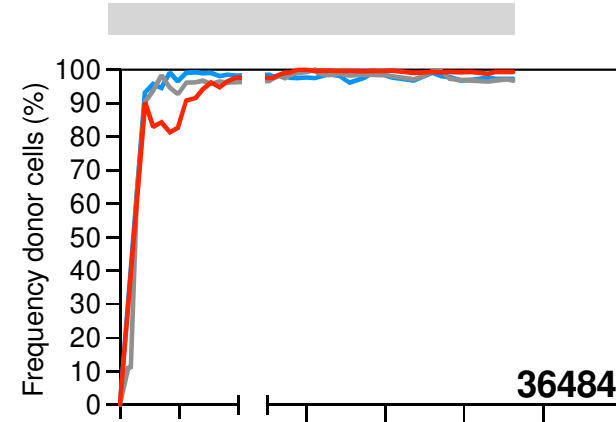
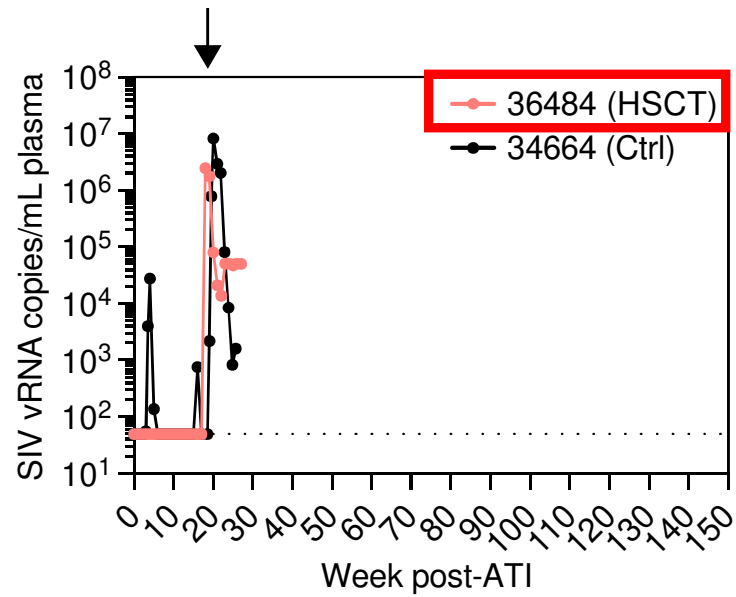


CD8 depletion in HSCT recipients versus controls

CD8a depletion period

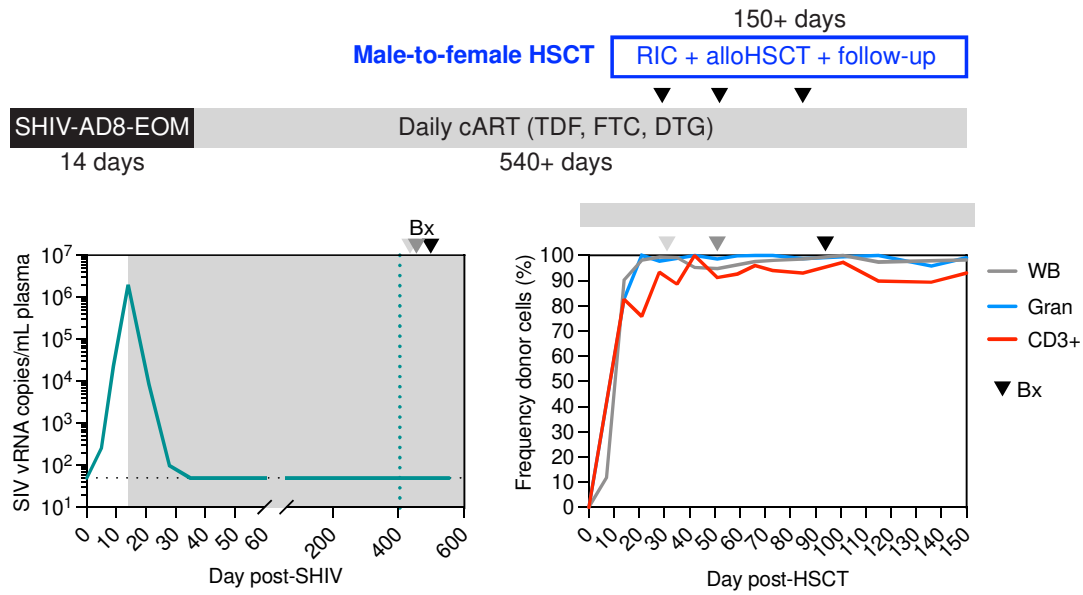


Why does virus persist?



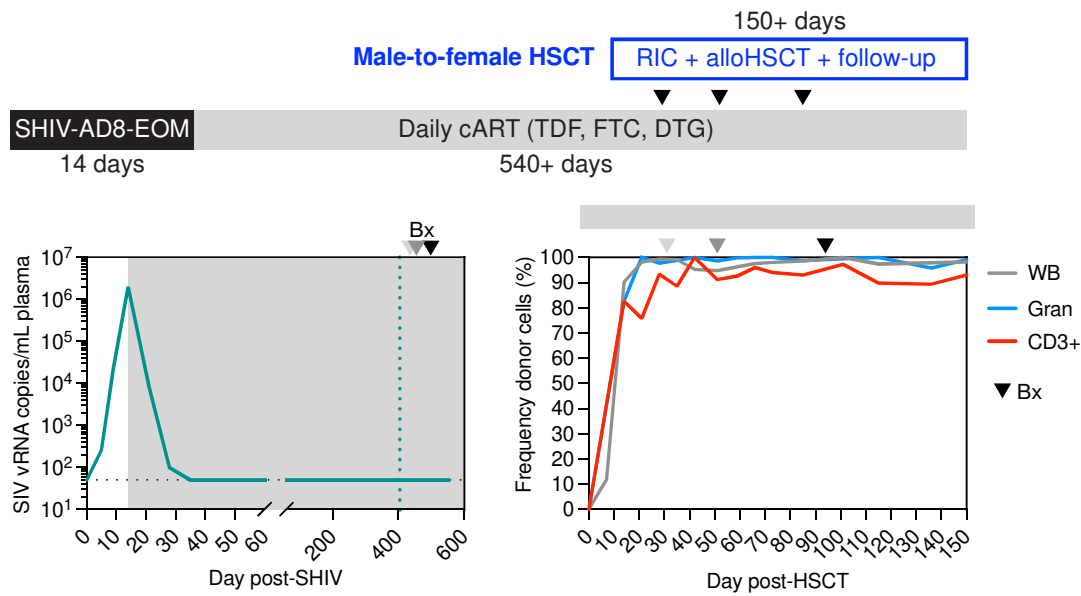
Why does virus persist despite alloimmunity?

Male-to-female HSCT

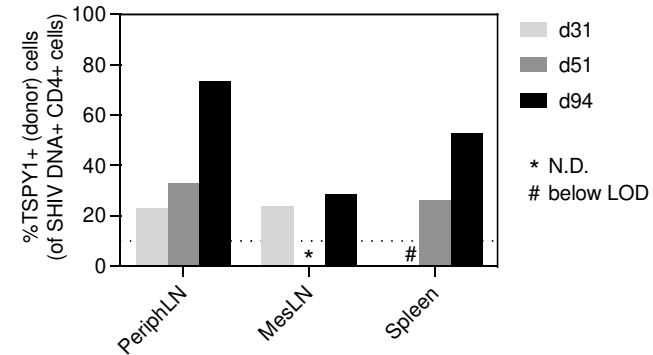
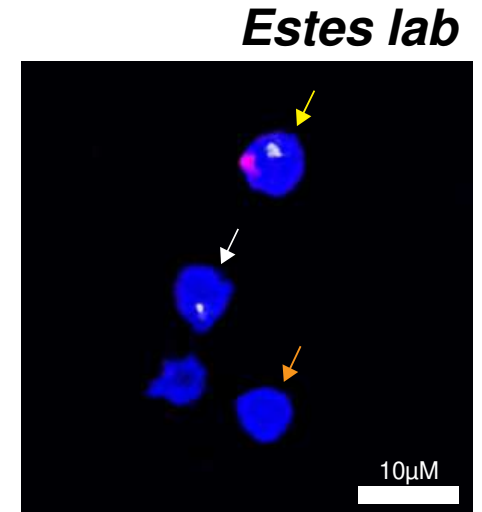
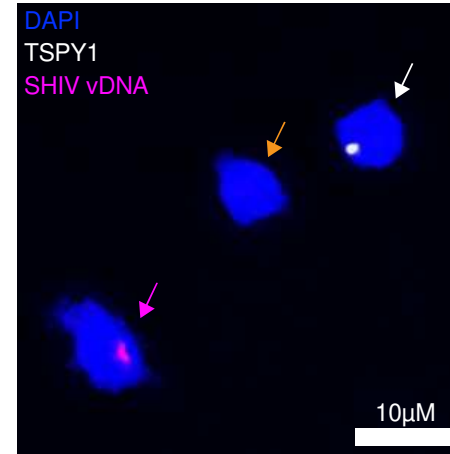


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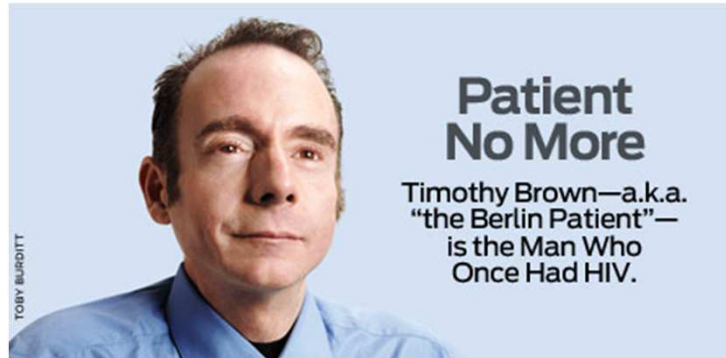
Male-to-female HSCT



PeriphLN CD4+ d51 post-HSCT

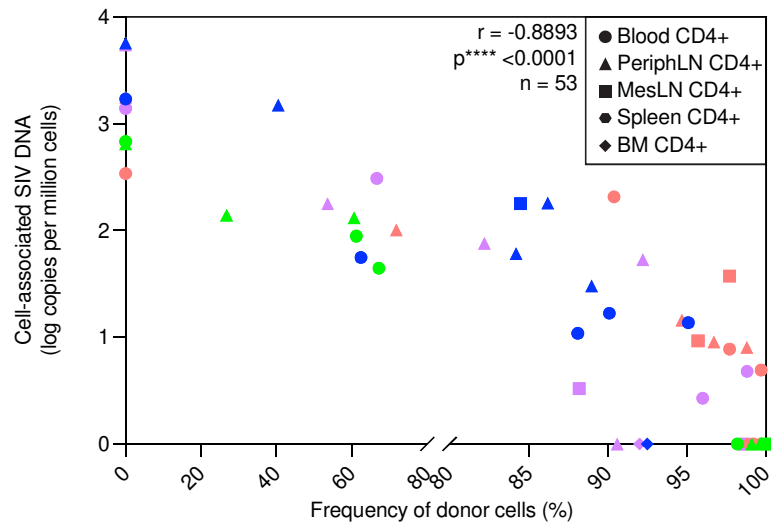


How does HSCT lead to HIV cure?

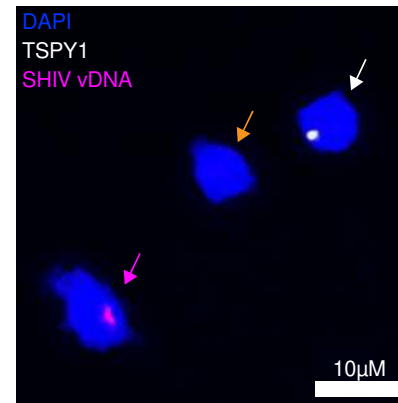


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- Graft-versus-host (Graft-versus-HIV) immunity
- CCR5 Δ 32/ Δ 32 graft

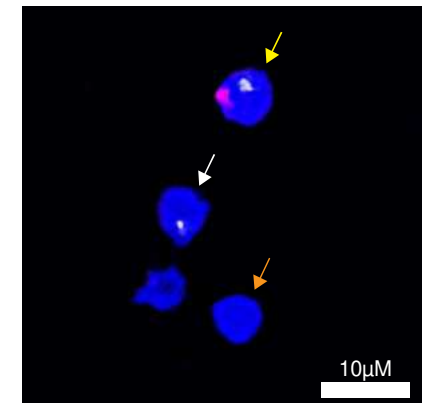
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Estes lab

