HIV-1 REMISSION WITH CCR5Δ32Δ32 HAPLO-CORD TRANSPLANT IN A U.S. WOMAN: IMPAACT P1107

Yvonne Bryson, MD

David Geffen School of Medicine at UCLA and Mattel Children's Hospital, Los Angeles, California, USA

www.impaactnetwork.org/studies/p1107

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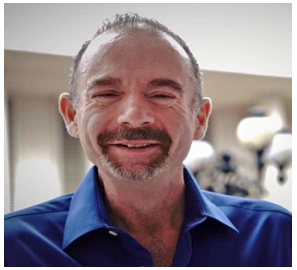
Cases of HIV-1 Cure

Berlin Patient (2009)



Timothy Ray Brown
(1966-2020)
Caucasian male
Provided proof-of-concept for cure with transplantation of CCR5Δ32/Δ32 cells

Strategy that led to cure

- Chemotherapy for relapsed AML
- Stem cell transplant x 2 (Chemo & TBI conditioning)
- Graft: **Adult donor CCR5Δ32/Δ32 bone marrow cells** (10/10 HLA match)
- Graft versus host disease
- ART stopped immediately after transplant
- HIV-1 remission **20 months; >12 years** (deemed cured)

Hutter G. et al. NEJM 2009 .
Hutter G. et al. AIDS 2011
Yukl SA et al. PLoS Pathog 2013

London Patient (2019)

Adam Castillejo
(40 years old)
Latino male

Strategy that led to cure

- Chemotherapy for Hodgkin's lymphoma
- Stem cell transplant (chemo conditioning)
- Graft: **Adult donor CCR5Δ32/Δ32 homozygous peripheral blood stem cells (9/10 HLA match**)
- Graft versus host disease
- ART stopped 16 months after transplant
- HIV-1 remission **18 months; 30 months (deemed cured)**

Gupta R.K. et al. Nature 2019
Gupta R.K. et al. Lancet HIV 2020; 7: e340–47

Why Only Two Cases of HIV-1 Cure Following Transplantation?

MAJOR ROLE of CCR5Δ32/Δ32 cells

- Mutation is rare (<1%)
- Most common in Northern Europe, **No routine screening of BM or donors**
- **Cord blood banks** as a potential solution

Adult unrelated donor grafts vs. cord blood donors

Advantage: High cell dose and rapid engraftment

Disadvantage: Stringent HLA match needed because of risk for GVHD

Umbilical cord blood grafts

Advantages: Banked and therefore readily available for screening, less stringent HLA match needed because of lower risk for GVHD

Disadvantages: Lower cell dose, delay in engraftment

Potential solution: Combined haploidentical cord grafts

Adult graft assures accelerated engraftment until cord graft takes over

Van Besien K and Childs R, Semin Hematol, 2016

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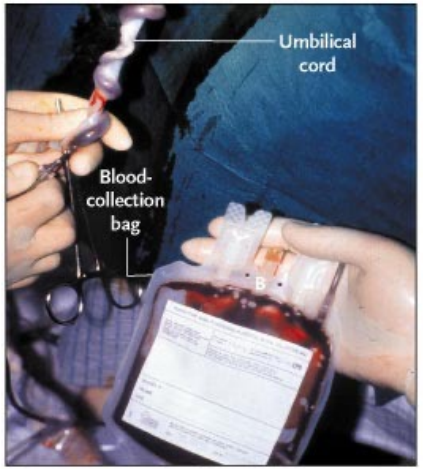
- Observational study
- Cord blood transplantation with CCR5Δ32 donor cells
- Children (>12 months of age) and adults living with HIV-1 requiring transplantation for other underlying diseases (cancer or hematopoietic diseases)
- Designed to use **previously screened cord blood units for transplantation (StemCyte Inc.**); maintain =>300 CBU prescreened for **CCR5Δ32Δ32**
- Collaboration between IMPAACT and the Center for International Blood and Marrow Transplant Research (CIBMTR); co-endorsed by ACTG



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Laboratory Studies of HIV-1 Persistence

- Chimerism-donor cell engraftment -cord blood unit
- HIV-1 cellular immune responses and inflammatory markers
- HIV-1 biomarkers
  - Plasma viremia (clinical and single copy assay)
  - HIV-1 total DNA levels (ddPCR)
  - 2-LTR circles (ddPCR),
  - Latent reservoir size (IUPM)
  - HIV-1 tropism-pre-transplant , *in-vitro* infection with R5- and X-4-lab strains, and autologous virus
- HIV-1 Antibody responses (Western blot-Bio rad)
- Antiretroviral drug levels –post ATI

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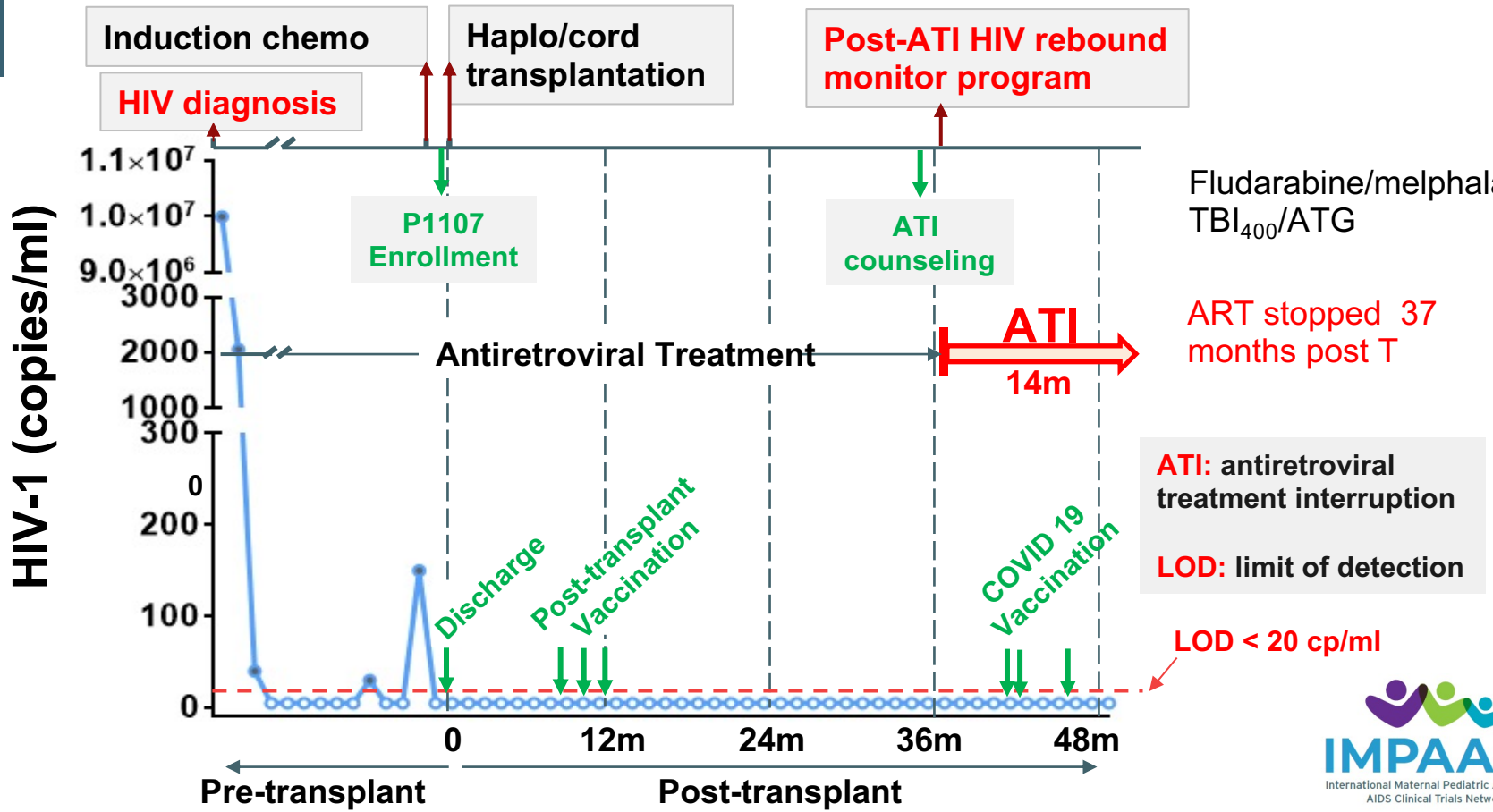
CASE REPORT

- Female; mixed race
- DX acute HIV-1 (2013)
- High-risk AML monosomy 7 (2017)
- 3-partially matched CCR5 delta 32/32 cord units (StemCyte)
- Haplo-cord transplant:5/8 match CBU & relative's PBMC (2017)

HIV-1 and AML Treatment Course



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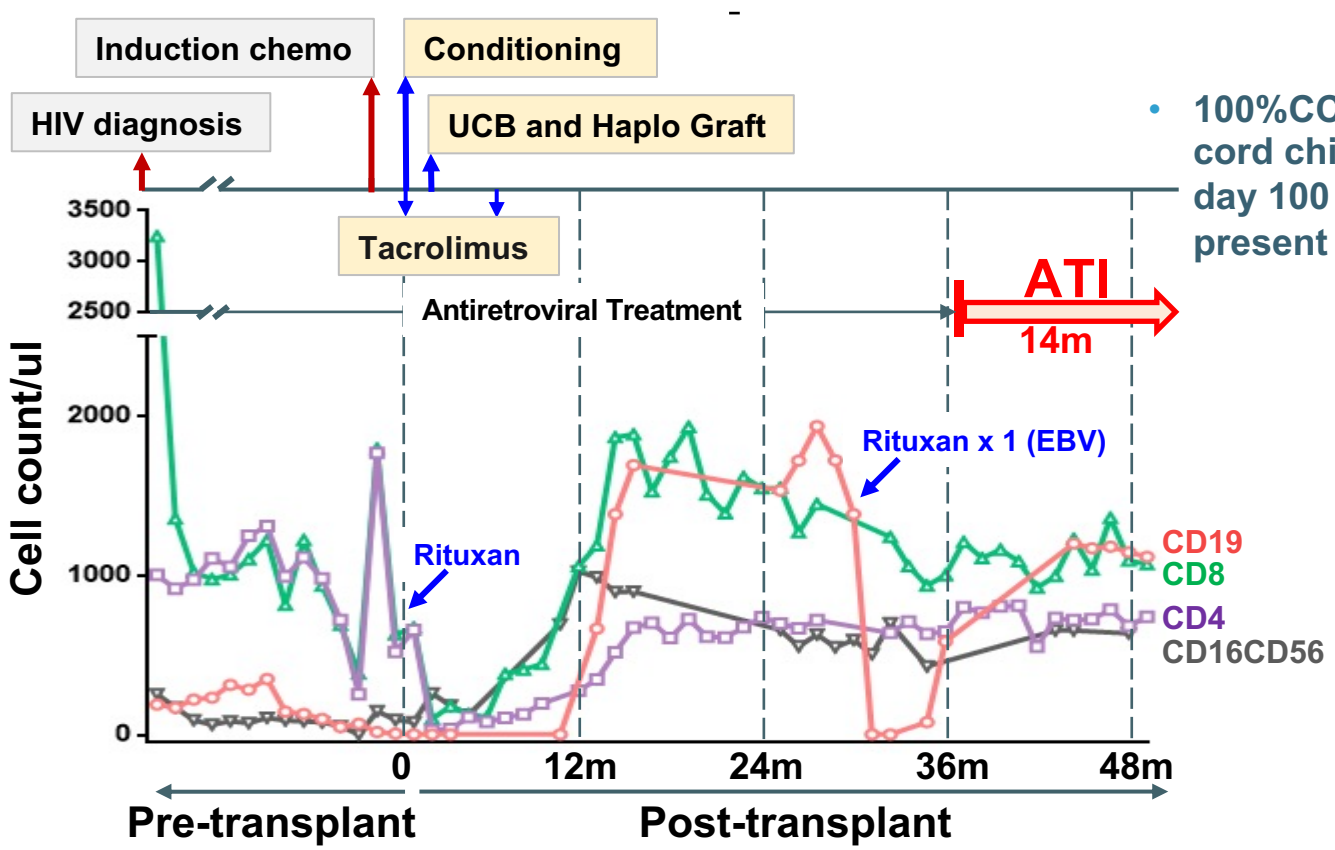
Immune Reconstitution Profiles



- 100%CCR5Δ32/Δ32 cord chimerism by day 100 until present

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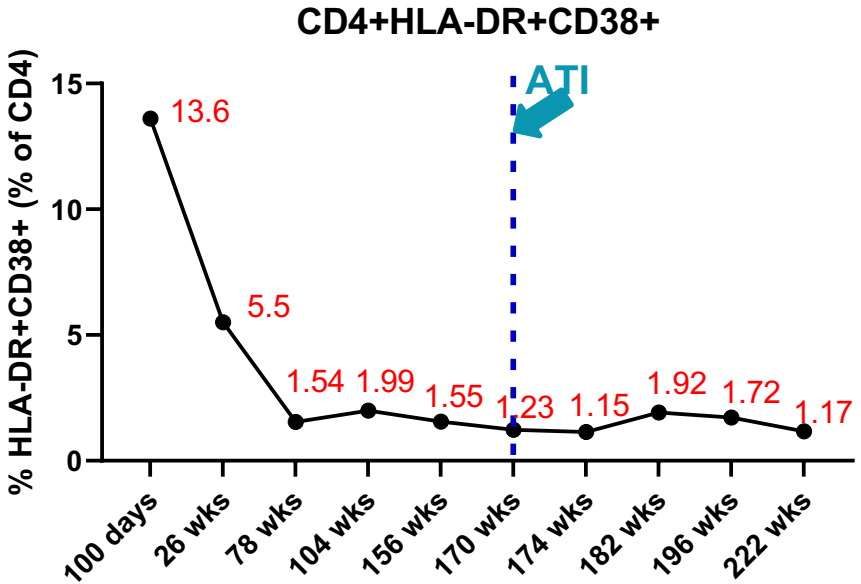
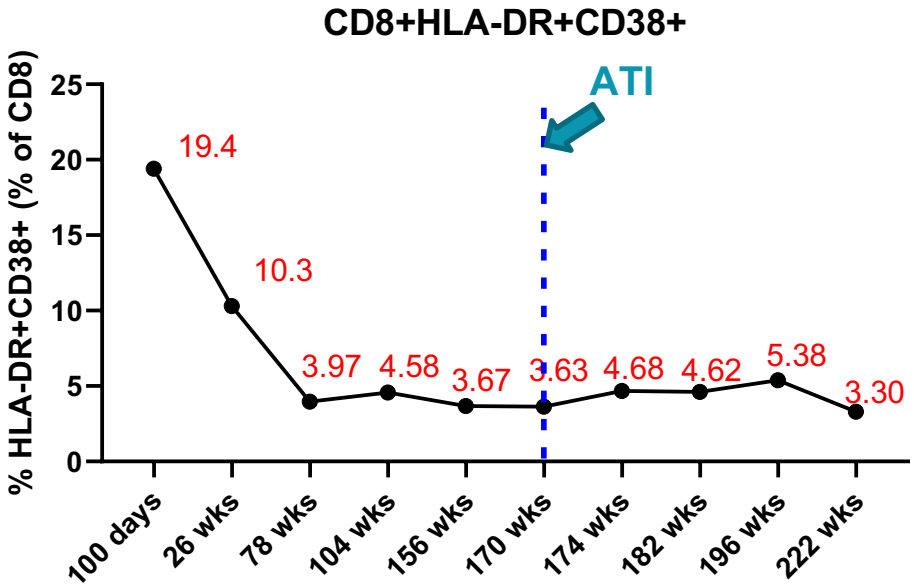
Decrease Immune activation of CD4 and CD8 T cells





No HIV-1 antigen (HIV-1 gag)-specific T cells were detected, while polyclonal responses (SEB) were intact.- data not shown

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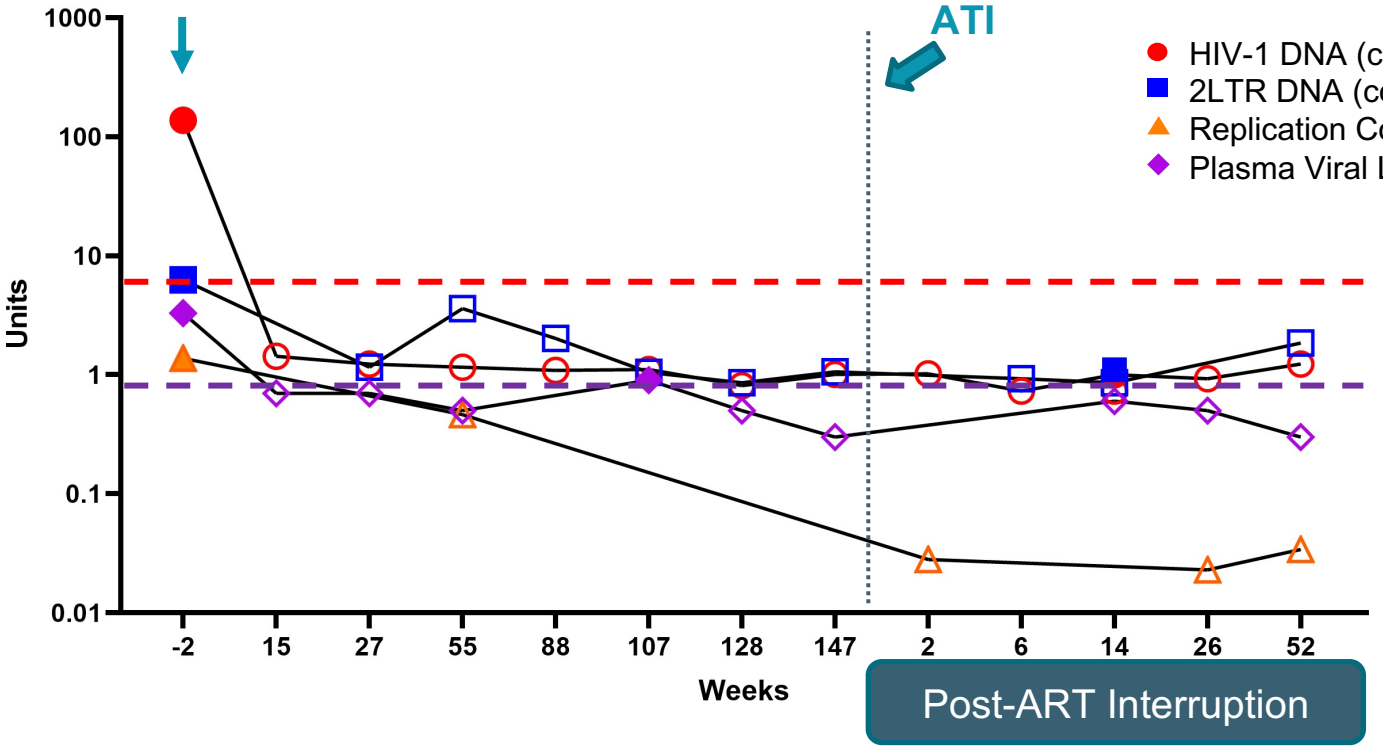
Cell-Associated HIV-1 DNA Levels, Latent Reservoir Size and Low-level Viremia Pre-and Post-Transplantation and Following ART Interruption

Pre-Transplant

Post-Transplant



HIV- 1 DNA
LOD <4.09 c/10^6 cells

Single copy
plasma viral load
(<0.5-<0.9 c/mL)

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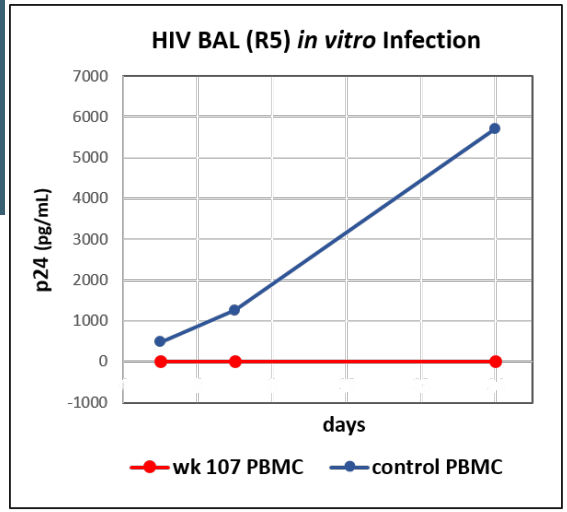
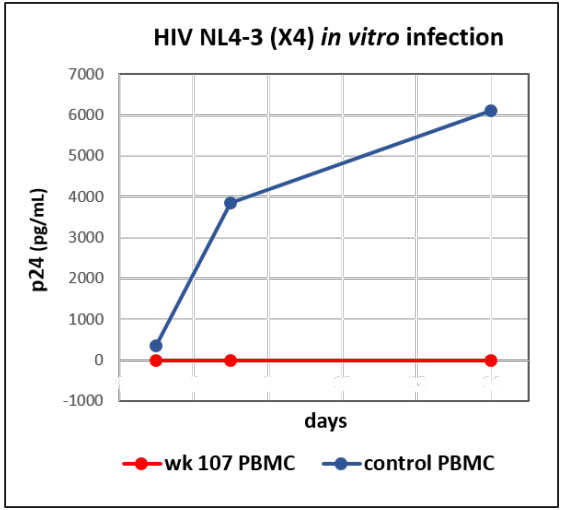
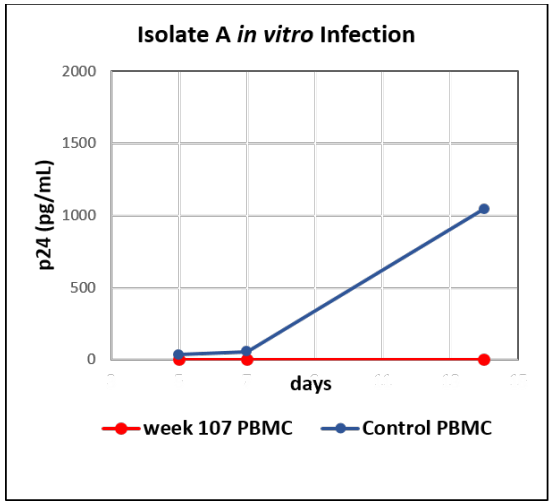
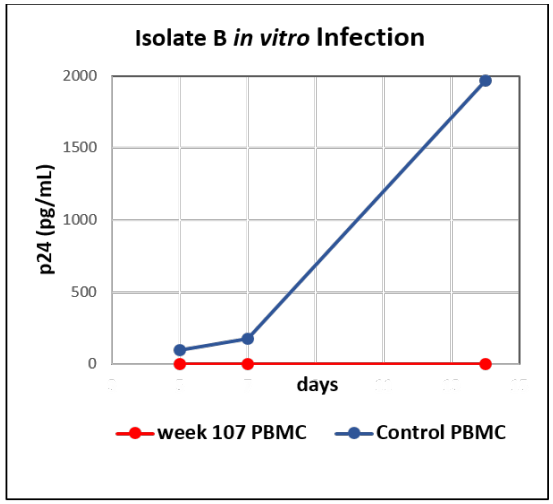




Ex-Vivo Resistance to CCR5- and CXCR4-tropic HIV-1





Ex-Vivo Resistance to Autologous Latent Reservoir Isolates

CCR5-Clade B virus

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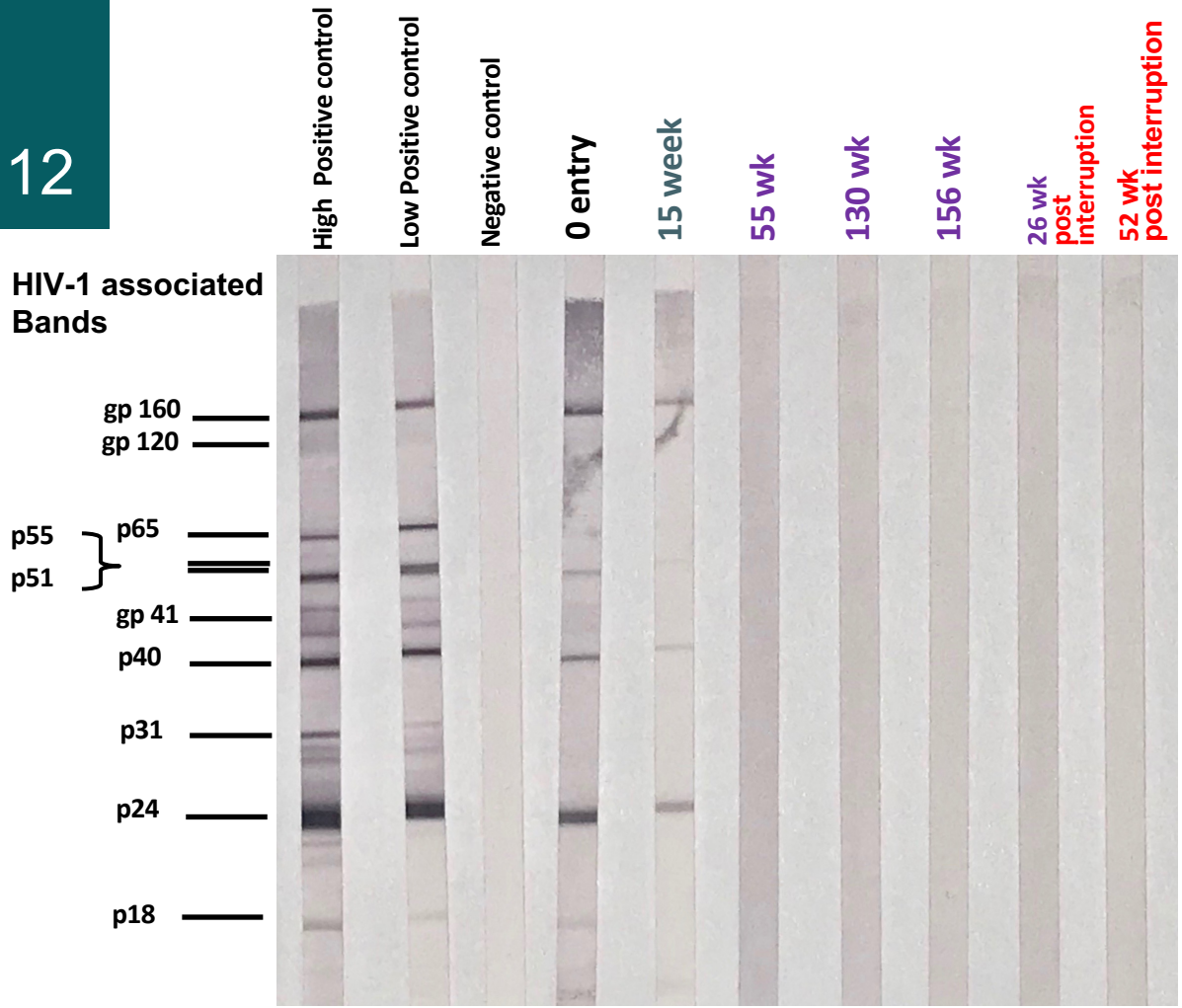

Loss of HIV-1-specific antibody responses by Week 55 post-transplant through 52 weeks post-ATI

IMPAACT P1107: Conclusions

- **First US woman of mixed race** living with HIV-1 successfully transplanted with CCR5Δ32/Δ32 haplo-cord SCT with 100% sustained engraftment of cord blood and in HIV-1 remission
- Durable remission of AML 4 years 6 months post SCT
- **14 months off ART; no viral rebound (no ARV's in plasma)**
- **No detectable replication-competent latent reservoir** (74.5 million CD4+ T cells analyzed)
- **Undetectable HIV-1-specific cellular immune** responses and **HIV antibody negative; *in-vitro* resistance to lab & autologous virus**
- Negative-(transient trace) HIV-1 DNA by ddPCR
- Remains clinically well with **NO GVHD**

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IMPAACT P1107: Conclusions

- **PROVIDES HOPE** for use of cord blood cells or halpo-cord to achieve HIV-1 remission for individuals requiring transplantation for other diseases

- Additional proof that HIV-1 reservoirs can be cleared sufficiently to afford remission/cure in the setting of resistant target cells

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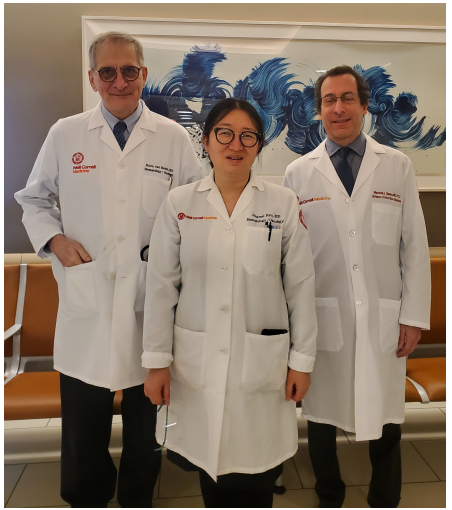

Protocol Team: NIAID MO: Renee Browning, NICHD MO: Rohan Hazra, Patricia Anthony, Koen Van Besien, Fredrick Bone, Anne Coletti, Marshall Glesby, Amanda Golner, Theodore Moore, Savita Pahwa, Lawrence Petz, Nicole Tobin, Meredith Warshaw, Elizabeth Smith

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