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288 Day Drug-Free Remission From HIV Rebound by Allogeneic PBSCT

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Case Presentation

- 55 YOM diagnosed with HIV in 1990; began cART in 1999 when CD4 T cell count decreased to 300 cells/mm^3.
- cART was stopped between 2004 and 2009, then restarted with TDF/FTC/ATV/r.
- April 2013, diagnosed with B-lineage acute lymphoblastic leukemia with myeloid features.
- Due to persistent low level viremia (plasma HIV RNA viral load 90-107 copies/ml) and in anticipation of myeloablative chemotherapy, cART was switched to TDF/FTC/RAL/ETR.
- October 2013, underwent reduced intensity conditioning with fludarabine and melphalan, followed by a 6/6 HLA-matched, related-donor, allogeneic PBSCT from a CCR5 WT donor.
- At the time of his transplant, the CD4 T cell count was 288 cells/mm^3 and the plasma HIV RNA viral load was 25 copies/mL. The patient remained on stable uninterrupted cART after PBSCT.
- Post-transplant course complicated by *E. coli* septicemia and *Pneumocystis jirovecii* pneumonia.
- Developed colon biopsy proven grade 1 GVHD at month 4, which was not treated with augmented immunosuppression.

Figure 1. Decrease in HIV Reservoir after PBSCT

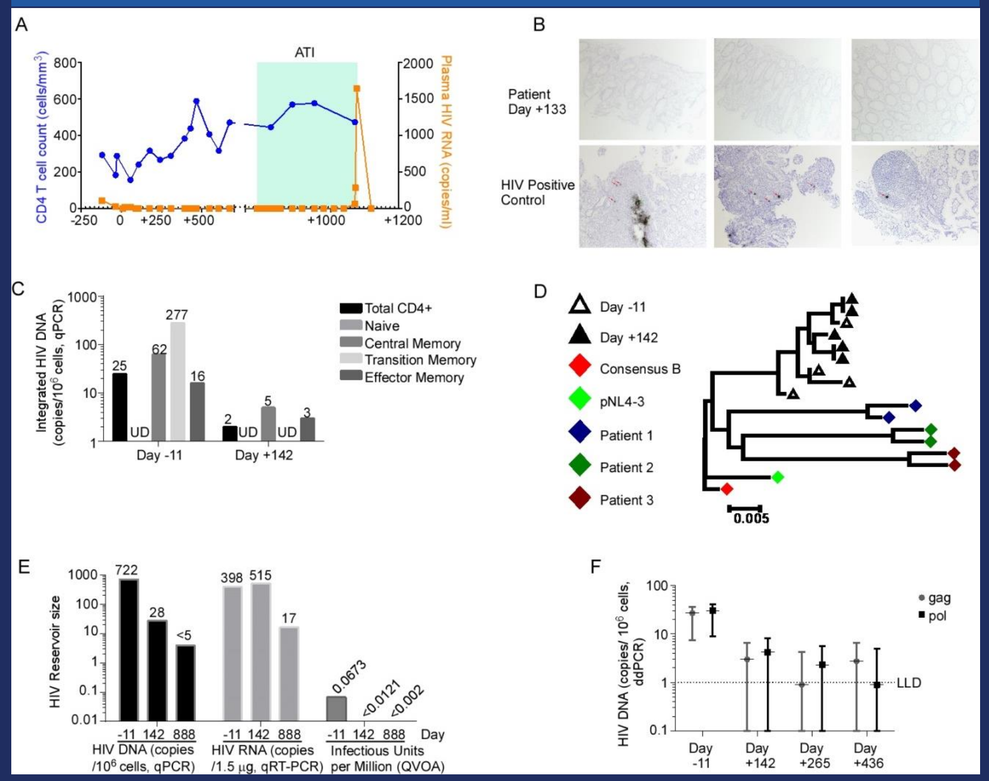
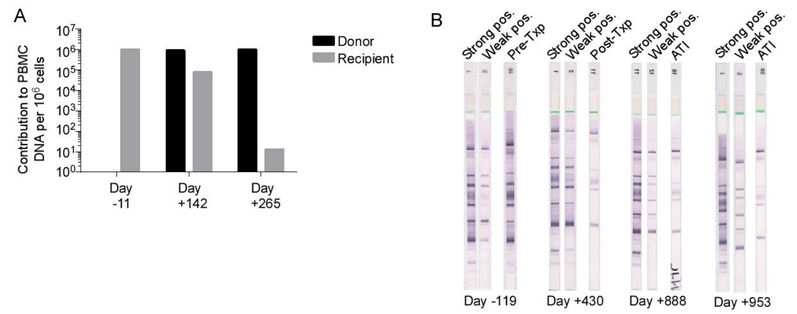


Figure 2. Decrease in anti-HIV immunity



Analytic Treatment Interruption

- At day +784 (Figure 1A), an ATI started according to a Mayo Clinic IRB approved protocol (15-001678).
- Plasma HIV RNA was monitored and undetectable Q2 wks for 12 wks, then Q4 wks .
- At day 288 of the ATI, asymptomatic viral rebound occurred at 60 copies/ml. The plasma HIV RNA rose to 283 copies/ml on ATI day 289 and 1640 copies/ml on ATI day 293, necessitating re-institution of cART.
- Viral genotype revealed no resistance associated mutations. The patient denied any potential HIV exposure to explain a potential new infection. Reinstitution of cART resulted in suppression of detectable viral replication after 4 wks.

Results (Figure 1)

- Plasma HIV RNA viral load was undetectable (<10 copies/mL) at day +4 post transplant, was detectable but below the LOQ (<20 copies/mL) on days +15 and +56, but again became undetectable by day +91 and remained undetectable through follow up (Figure 1A).
- Clinical peripheral blood HIV proviral DNA by Roche Amplicor HIV-1 Proviral DNA Test, which was positive pre-transplant, became undetectable by day +56 and remained undetectable through day +604, when the assay was no longer commercially available.
- HIV RNA was undetectable by ISH of 105 total colon biopsy sections obtained on day +133 for evaluation of GVHD-associated diarrhea (Figure 1B).
- The patient underwent leukapheresis on day -11 pre-transplant, and on days +142, +288, +436 and +888. Multiple measures of HIV reservoir size in peripheral blood cells revealed significant reductions in reservoir size (Figure 1C, E and F).
- Single genome sequencing and phylogenetic analysis identified identical clones at day +142 (Figure 1D), possibly consistent with homeostatic proliferation of latently infected cells in the post-transplant period.

Results (Figure 2)

- Microchimerism evaluation revealed 8% of DNA in circulating CD4 T cells at day +142 was of recipient origin, during the time when the patient was experiencing clinical GVHD (Figure 2A). By day +265, only 0.0013% of circulating CD4 T cell DNA was of recipient origin, or 13 per 10^6 cells.
- Consistent with the “Berlin patient” (PLoS Pathog. 2013;9(5):e1003347.), our patient demonstrated devolution of anti-HIV antibodies, as demonstrated by decreasing number and intensity of anti-HIV bands on western blot from day -119 to day +888 (Figure 2B).

Conclusions

- Allogeneic PBSCT in the setting of HIV is associated with significant reductions in HIV reservoir size by multiple measures, including prolonged cART free remission.
- Allogeneic PBSCT in the setting of suppressed viral replication may be associated with loss of HIV-specific immunity. Further immunologic studies are underway.
- We hypothesize that immune activation in the setting of GVHD without anti-HIV specific immunity may cause homeostatic proliferation of latently infected cells, decreasing the chance of HIV eradication.

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