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HIV rebound and meningoencephalitis following ART interruption after allogeneic hematopoietic stem cell transplant: an investigation of the source of HIV rebound

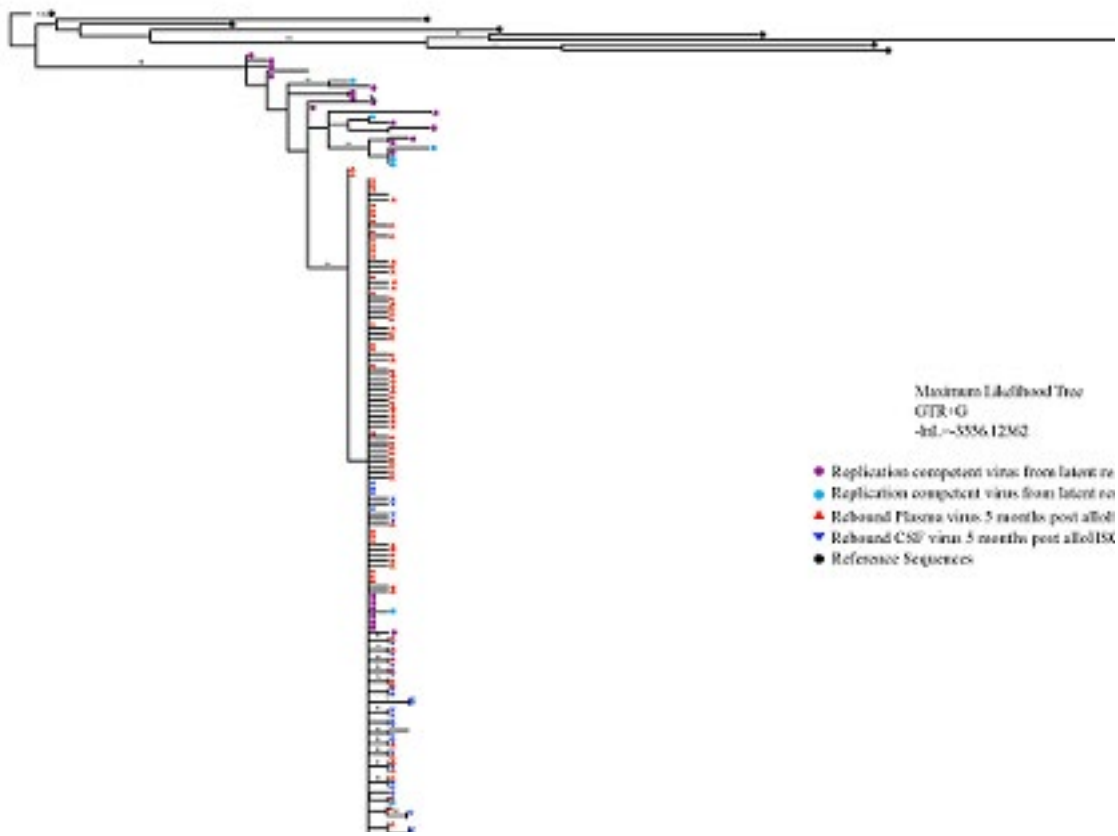
A. Capoferri[1,2], M. Sievers[2], A. Redd[2,3], A. Cash[2], D. Xu[2], S.F. Porcella[3,4], T. Quinn[2,3], R.F. Siliciano[1,2], M. Levis[2,5], R.F. Ambinder[2,5], C.M. Durand[2,5]

[1]Howard Hughes Medical Institute, Baltimore, United States, [2]Johns Hopkins University, Department of Medicine, Baltimore, United States, [3]National Institute of Allergy and Infectious Disease, National Institutes of Health, Division of Intramural Research, Bethesda, United States, [4]Rocky Mountain Laboratories, Genomics Unit, Research Technologies Branch, Hamilton, United States, [5]Sidney Kimmel Cancer Center, Baltimore, United States

Background: Allogeneic hematopoietic stem cell transplant (alloHSCT) with uninterrupted antiretroviral therapy (ART) is being investigated as a component of HIV eradication strategies. In the two "Boston patients", alloHSCT resulted in the disappearance of HIV in peripheral blood. However, after analytical ART interruption, viral rebound occurred. Proposed sources of HIV rebound include the latent reservoir in resting CD4+ T cells and tissue macrophages. We present the case of an HIV-infected patient who received alloHSCT for leukemia and experienced acute retroviral syndrome after self-discontinuing ART post-alloHSCT.

Methods: Resting memory CD4+ T-cells obtained 16 and 1 week prior to alloHSCT were used in a limiting-dilution viral outgrowth assay (VOA) in which each well that demonstrates viral growth contains a single replication-competent viral clone. The pol region of virus from positive VOA supernatants was sequenced. Rebound virus from blood and cerebrospinal fluid (CSF) was also analyzed using deep-sequencing (Roche 454) of pol. Sequences were aligned and maximum likelihood analysis was performed using the GTR+G model of evolution with 100 bootstrapping pseudoreplicates.

Results: The patient had undetectable plasma HIV and achieved 100% donor chimerism at week 12 post-alloHSCT, but then became non-adherent with ART. At 5 months, the patient presented with fever and meningoencephalitis. Plasma and CSF HIV levels were 25,500 and 17,000 copies/ml, respectively. Before alloHSCT, 31 sequences were isolated from the VOA. At rebound, 14,645 and 5,003 sequence reads were obtained from CSF and blood respectively, and were combined into consensus sequences using a cut-off of >0.2% of total sequence reads. An identical sequence found at both pre-alloHSCT timepoints accounted for 9/31 (29%) of independent VOA sequences. This sequence grouped with the plasma and CSF viral rebound sequences in a monophyletic clade with high sequence homology.



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Conclusions: Despite 100% donor chimerism in peripheral blood, ART interruption led to HIV rebound in plasma and CSF. Rebound virus was identical to a pre-alloHSCT isolate which compromised nearly 1/3 of the latent CD4+ T-cell reservoir sampled. This unique case suggests that recipient cells persist at early time-points after alloHSCT and that a single viral population latent in resting memory CD4+ T cells can re-establish infection.