Functional cure after long term HAART initiated during early HIV infection - a case study.

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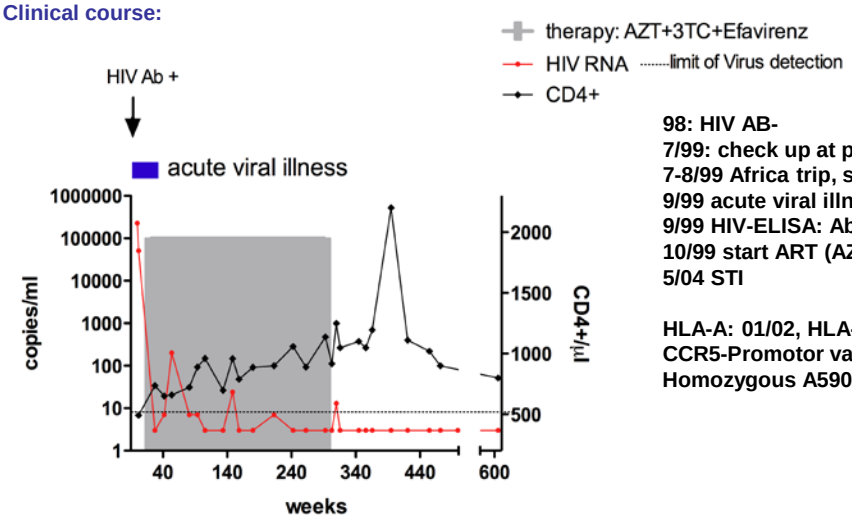
Abstract:

Background: Early initiation of cART during acute HIV infection can lead to control of viral replication after cessation of therapy in a rare subgroup of patients termed post treatment controllers (PTC). We set out to define immunological and virological correlates of post treatment control and to assess the potential of eradication vs. functional cure.
Methods: A 67 yrs. old male was treated with cART ca. 3 months after HIV exposure and 1 month after seroconversion for a total of 5,5 yrs.; cART was stopped in May 2004 and the patient remained BLOD(< 20 c/ml) and shows normal T cell counts and distribution without ART since 9 years. We performed comprehensive analyses to assess the immuno-virological correlates of PTC including a humanized mouse model in this patient.
Results: CD4 count is stable between 800-1000 cells/µl, the homozygous CCR5 promoter variant A59029G but no delta 32 deletion was detected, HLA-I subtype was A 01, 02 B: 44, 52; no viral RNA or DNA was detected using ultrasensitive techniques in plasma or PBMC. ELISPOT revealed broad CTL responses against gag and nef epitopes and we could detect HIV specific CD4 proliferative responses. We find a normal distribution of TEM and TCM comparable to a control group of nine elite controllers (EC) (data not shown). The frequency of peripheral Treg cells was comparable to normal controls and EC (data not shown). Eventually virus could be recovered in vivo in a Rag2$^{-/-}$yc$^{-/-}$ (Rag-hu) humanized mouse model after transplantation of purified donor CD4 T cells and anti CD3/CD28 stimulation indicating the persistence of replication competent virus (data not shown).
Conclusion: The data obtained in this unique case suggest a functional cure of this patient rather than viral eradication after early onset cART. The presence of strong HIV specific T cell responses, normal frequency of regulatory T cells and animal data suggest a strong role of preserved adaptive immune responses as a correlate of viral control in this patient. Subsequent virological and immunological studies should look into the correlate of viral control in this and other PTC patients.

Clinical course:



98: HIV AB-
7/99: check up at primary physician: in good health
7-8/99 Africa trip, sexual transmission most likely
9/99 acute viral illness/lymphadenopathy
9/99 HIV-ELISA: Ab + (WB: few bands, immunfluorescence neg)
10/99 start ART (AZT/3TC/EFV, later switched to TDF/FTC/EFV
5/04 STI

HLA-A: 01/02, HLA-B: 44/52
CCR5-Promotor variant:
Homozygous A59029G

Figure 1 (clinical course): Here, we present data of unique case of a post treatment controller with undetectable viral loads after early ART treatment was stopped after 5 years in 2004. Remarkably, the viral load of this patient has stayed below the level of detection with stable CD4+ counts for more than nine years. This patient was further analyzed for host factors but neither the HLA molecules (HLA A 01,02, B44, B52) nor a deletion of the CCR5 receptor could account for the control of the virus after treatment interruption. No viral RNA was detected at any time point later than 3 mths. post STI using ultrasensitive assays and no proviral DNA was found in PBMC. Colon biopsies were staining negative for p24 Ag and no viral RNA was found in CSF. No viral replication was detected after ex vivo stimulation of PBMC using standard techniques. However, virus was recovered using prolonged ex vivo stimulation with repeated addition of stimulated donor cells. HIV replication was detected after transplanting the patient`s CD4+ T cells into Rag2-/-yc-/- (Rag-hu) humanized mice indicating replication competent virus. Sequencing of these viruses is currently ongoing, preliminary analysis shows CCR5 co-receptor usage.

Results:

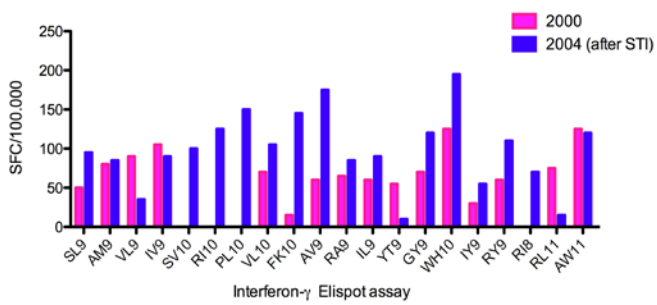


Figure 2: Broadly directed CD8+ T cell responses can be detected in a standard Elispot assay using HIV CD8+ optimal peptides.

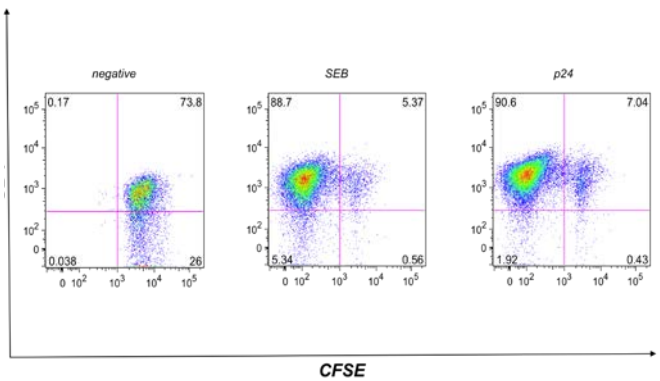


Figure 3: Strong proliferative HIV-specific CD4+ T cell responses can be detected in the standard CFSE proliferation assay.

Conclusions: This case shows that a functional cure may be achieved in individual cases after early treatment of HIV infection. Broad HIV specific T cell responses seem to be associated with post treatment control of viral replication. No beneficial HLA haplotypes were detected in this patient.

Further reading:

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study, Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, et al. (2013) Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study. PLoS Pathog 9(3): e1003211. doi:10.1371/journal.ppat.1003211

Acknowledgements

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