Introduction

HIV displays significant diversity due to its high replication rate and its ability to adapt to evade the host immune response. HLA-associated HIV adaptations are observed at a population level 1 and at an individual level. This poses a significant challenge for design of immunogens in therapeutic vaccines which involve the induction of HLA class 1 restricted CD8 T cells to clear archival virus from adventitiously-infected CD8 T cells in the context of HAART. Clonality of the archived virus will be dependent on the level of mutational escape present prior to therapy initiation. However there is limited data available on the occurrence of the first immune escape following HIV transmission, the magnitude and frequency of the initial immune response that induces clonal escape and the mechanisms of viral adaptation after infection. The staging of acute HIV infection has improved with the implementation of newer laboratory assays, new enabling studies of patients experiencing acute and early HIV infection. This study aimed to investigate:

- The timing of the initial immune response following acute HIV infection
- The first HIV adaptations induced by the initial T cell responses
- The dominant HLA targets of the first immune response

Study group

12 patients were identified at presentation during acute or early HIV infection and are shown by Fiebig staging below (Figure 1). PBMC and plasma samples median 1-7 samples/patient were collected and stored. Dates of HIV transmission were defined by epidemiological studies in 6/12 patients (27, 37, 40-57, 84-93 days post HIV transmission.)

Methods

HIV sequencing: HIV full genome sequences were determined in plasma samples from 12 patients using 454 deep pyro-sequencing (Roche FLX). HIV sequences were aligned using HXB2 and reference sequence. Individual patient sequences were further analysed for the presence of HLA-associated mutations in Gag and Nef using the IIID VGAS program which accelerated a database of HIV known HLA associated adaptations derived from large population studies (1). The mutations were plotted in relation to time from Indeterminate Group 4 weeks (2).

Results

Overall 178 IFN-γ responses were determined in PBMC samples across the 12 patients in the first sample collected. Gag and Nef HIV peptide induced the highest magnitude IFN-γ responses and the highest frequency responses (Figure 2).

When the 12 patients were assessed individually for HIV peptide responses (Figure 3), Gag (11/12) and Nef (12/12) responses were detected in the majority of patients (Figure 3a). Gag and Nef peptides also induced higher magnitude responses in most patients (Figure 3b). T cell responses were detected in samples from patients 27-57 days post known HIV transmission date.

Conclusions

In summary, T cell responses were detected within 27 days of known HIV transmission date. The proportion of detectable responses increased significantly over time while the magnitude of the responses decreased over time. Gag and Nef induced the highest number of responses and the highest magnitude of responses. In addition, while the majority of HLA associated mutations detected in early infections were not patient HLA restricted, and therefore may include adaptations induced by the pre-exposure host or host, small numbers of patient HLA restricted adaptations were detected as early as 27 days post infection in one case and within 5 days of an Indeterminate WB in a second case.

In conclusion, CDb T cell responses induced by incoming virus select for HLA-associated mutations in acute and early HIV infection. These findings have implications for the efficacy of CD8 T cells induced by a therapeutic vaccine to clear HIV infection, unless the immunogen takes early mutations in account.

References

3. Adaptation of HIV to human leucocyte antigen polymorphism.

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