Introduction:
Identification of the earliest CD8 T cell responses against HIV may help select or exclude critical viral targets for inclusion in an HIV vaccine. Here we describe the dynamics of the earliest detected HIV-specific CD8 T cell responses and infections in the HIV population sequences encoding the targeted epitopes in a 43 year old female who presented 27 days after a known date of HIV sexual transmission with a CD4 T cell count of 225 cells/µL and an HIV RNA viral load of >1 million copies/mL in Fiebig stage II, with acute clade C HIV-infection. The patient was heterozygous for the delta 32 CCR5 gene and expressed the HLA-alleles:

HLA-A*01, A*02, B*07, B*08, C*07

Materials and Methods:
T cell responses
Cryopreserved peripheral blood mononuclear cells collected on days 27, 34, 42, 48, 90, 118 and 223 post-transmission (PT) were evaluated for HIV-specific CD8 T cell responses by IFN-γ ELISPOT against 64 HLA class 1 restricted HIV peptides (all known + 16 novel peptides) based on the patient’s HLA class 1 alleles. The IFN-γ ELISPOT assay was performed as shown in Fig 1) and as previously described (1). ELISPOT responses were defined as positive if > 50 spot/cell million (SPU) after background subtraction.

HIV sequencing
Full length HIV genome sequencing of Gag, Pol, Nef and Envelope proteins was performed using 454 deep pyro sequencing (Roche FLX) on six longitudinal plasma samples collected on days 27, 34, 42, 48, 90 and 118 PT.

Clinical Progression
At first presentation 23 days after likely date of HIV transmission from a known donor, p24 antigen was present but p24 antibody was negative by ELISA and Western blot. HIV RNA was detected in plasma by day 27 PT and the first PBMC sample was collected at this point. The ELISA became reactive and the Western blot indeterminate (p160+, p24+) when samples were tested a week later, suggesting Fiebig stage IV. The Western blot tested positive three months later (including p31+) on day 118 and the patient was classified as Fiebig stage VI. The patient commenced treatment on day 231 when the CD4 T cell count dropped from 756 to 560 cells/µL. The HIV RNA was undetectable (>40 HIV RNA copies/mL) when tested on day 272 PT.

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Results

Figure 2 The clinical progression of the patient is illustrated here from initial presentation to day 227 post HIV sexual transmission, ART = Combination antiretroviral therapy, TFC = l'antiviral, ABC = Abacavir, RAL = Raltegravir

Don 23 - p24(antigen) antibody negative by Western Blot (Fiebig stage II)
Don 32 - p24 antigen, Viral RNA >1 million copies/mL
Don 42 - p24 antigens; gp160 abs, p24+ western blot indeterminate group 4 (Fiebig stage IV)
Don 118; p24 antigen + Western Blot positive with p31+ (Fiebig stage VI)

Summary and Conclusions
Changes in early CD8 T cell immunodominance hierarchy were apparent in this case with known date of transmission and testing prior to development of the antibody response. Env and Gag epitopes were the earliest targets of T cell responses. Subsequent broadening of the CD8 T cell response was observed but was not associated with prominent mutational escape (only 2 of 25 targeted epitopes) evident by deep parallel sequencing. In addition, there was no evidence of donor reversion in epitopes not restricted by the patient’s HLA alleles, suggesting that donor virus may have been already well adapted to the patient’s CD8 T cell immune response.