What Is the Most Important for Elite Control: Genetic Background of Patient, Genetic Background of Partner, both or neither? Description of Complete Natural History within a Couple of MSM

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Background: We describe a homosexual man who strongly controlled HIV-1 for ten years despite lack of protective genetic background.

Methods: HIV-1 DNA was measured in blood and other tissues. Cell susceptibility was evaluated with various strains. HIV-1-specific (CD4 and CD8 activation markers and immune check points) and NK cells responses were assessed; KIRs haplotypes and HLA alleles were determined.

Findings: Two HIV-1 RNA copies/mL of plasma were detected in 2009, using an ultra-sensitive assay. HIV-DNA was detected at 1.1 and 2 copies/10^6 PBMCs in 2009 and 2015 respectively, at 1.2 copies/10^6 cells in rectal cells in 2011. WBs showed weak reactivity with antibodies to gp160, p55 and p25 from 2007 to 2014, remaining incomplete in 2017. CD4 T cells were susceptible to various strains including HIV-KON, a primary isolate of his own CRF02_AG variant. CD8 T cells showed a strong poly-functional response against HIV-Gag, producing mainly IFN-γ; a robust capacity of antibody-dependant cell cytotoxicity (ADCC) was observed in NK cells. Case patient was group B KIR haplotype. Neutralizing antibodies were not detected. CD4 and CD8 blood T cells showed normal proportions without increased activation markers. Phylogenetic analyses identified the same CRF02_AG variant in his partner. The patient and his partner were heterozygous for the CCR5Δ32 deletion and shared HLA-B*07, C*07 non-protective alleles.

Interpretation: This thorough description of the natural history of an individual controlling HIV-1 in various compartments for ten years despite lack of protective alleles, and of his partner, may have implications for strategies to cure HIV-1 infection.

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1. Introduction

Without antiretroviral therapy (ART), most individuals infected by human immunodeficiency virus type 1 (HIV-1) experience persistent viral replication and a declining CD4+ T cell count, leading to the acquired immunodeficiency syndrome within 10 years.

So-called elite controllers (EC) spontaneously control HIV replication, with low or undetectable HIV-1 RNA levels, strong HIV-1-specific CD8+ T cell responses, and normal CD4+ T cell counts. These individuals represent about 1% of all HIV-infected patients. Their viral load can only be detected by using ultrasensitive assays (<1 copy/ml). Viral sequencing usually reveals no consistent gene deletions or signatures associated with reduced replicative capacity. This spontaneous viral control seems to be driven by host gene polymorphisms such as the CCR5 Δ32 deletion or specific HLA class I alleles (B*27 or B*57) (Antoni et al., 2013), and by robust immune responses (Perereya et al., 2008), consistent with predominant linkage between the HLA class I locus and EC status (Xie et al., 2010).

Here we report the complete natural history of a very rare elite controller during a 10-year period of untreated infection. The patient was a homosexual man with a history of repeated unprotected receptive anal intercourse for ten months with his first and only (HIV-1-infected) partner. He differs from elite controllers reported in other studies by his lack of a (homozygous or heterozygous) protective HLA-class I allele (Bailey et al., 2008; Mendoza et al., 2012; Buckheit et al., 2012). We were also able to study the immunological and virological outcomes of his partner during the same period.

2. Case Report

A 25-year-old man was tested for HIV in November 2007, after reporting unprotected receptive anal sex with pre-ejaculatory fluid exposure from October 2006 to July 2007 with his first and only sexual partner. Both men were uncircumcised. Our case report declared that his first HIV test, in July 2006, had been negative. He was found to be HIV-1-positive by ELISA (HIV-2- and HTLV I/II-negative). HIV-1 WB showed first weak reactivity with antibodies to gp160, p55 and p25 from 2007 to 2014, then positive reactivity with antibodies to gp160, p55, gp41, p40, p24 and p18 and weak reactivity with antibodies to gp110 from three sera sampled between January and November 2015 retested simultaneously (Fig. 1a). In April 2017, HIV-1 WB remained incomplete with positive reactivity with antibodies to gp160, p55, gp41, p40, p24, p18, weak reactivity with antibodies to gp110 and no reactivity with antibodies to p68, p34 (Fig. 1a). Dates of serological, T-cell and antibody production.

HIV-1 RNA was measured by an ultrasensitive assay. Total cell-associated HIV-1 DNA in collected PBMC was detected using an ultrasensitive assay (Descours et al., 2012, Avettand-Fenoel et al., 2008). The techniques to isolate the virus from in vitro-stimulated total and CD4+ FACS-sorted T cells from blood and tissues and ultrasensitive assays have been previously described (Avettand-Fenoel et al., 2009).

The heat-inactivated serum was tested for neutralizing activity, starting the dilutions at 1:10, using the TZM-bl assay as previously described (Bouvin-Pley et al., 2013) and MN, BX08 and NL4-3 as a highly sensitive (tier 1) indicator strains (Simen et al., 2009).

Informed consent for participation in this research, including genetic analysis, was obtained from both men, in accordance with French ethical requirements and the Helsinki Declaration.

3. Methods

Serum was tested with the following assays: Genscreen Ultra Ag-Ab (Bio-Rad®), Biotest (DiaSorin®), Determine HIV-1/2 (Abbott®), Vidas HIV Duo (bioMérieux®), Vitros HIV1/2 assay (OrthoDiagnostiCs®), Vironostika HIV Uniform II Ag/Ab (Organon Teknika®), and HIV Architect Combo (Abbott®). Discrimination between HIV-1 and HIV-2 was achieved by using the ImmunoComb II HIV1/2 BiSpot (Origencis®). HIV-1 Western blot was performed using the New Lav Blot 1 (Biorad®). The partner’s genotype was analyzed with the ANRS-AC11 algorithm. HLA sequences were read with a LAbScan 200 (Luminex Technology) and computer-assisted HLA Fusion software. KIR genotyping was performed by PCR using standard primers, and internal controls (Vilches et al., 2007).

HIV-1-specific responses were evaluated first by using an IFN-γ ELISpot assay on PBMC and lymph node (LN) cells stimulated with 18 pools of 15-mer synthetic peptides targeting Gag, Reverse Transcriptase and Nef (Samri et al., 2006). Second multi-parametric flow cytometry was performed to further assess HIV-specific CD8 T cells by intracellular cytokine staining (ICS) of IFN-γ, IL2, TNFα and MIP1α, and CD40L expression after incubation with the HIV-1 peptide pools that had induced an IFN-γ ELISpot response (Cardinaud et al., 2011). A CMV peptide and staphylococcal enterotoxin B (SEB) were used as positive controls. Cells were stained with anti-CD3/PB, anti-CD8/APC-CY7, anti-IFN-γ/Alexa700, anti-TNFα/PCy7, anti-IL2/ APC (BD Biosciences®) and anti-CD4/ ECD (Beckman Coulter®) (Supplementary Fig. 1 Strategy of staining for poly-functional assays). Poly-functional NK was performed to simultaneously detect degranulation (anti-CD107a mAb, BD Biosciences) and cytokine production (intracellular expression IFN-γ (BD Biosciences) and TNF-α (E-Biosciences) (Béziau et al., 2012).

Finally, multi-parametric analysis of CD4 and CD8 blood T cells was performed for studying activation markers (HLA-DR, CD38, CD25, CD69) and immune check points (PD-1, TIM-3, CTLA-4) combined to anti-CD3, -CD4, -CD45RA, -CD27, -CCR7, -CXC5R, and -CD32. Data were acquired with a Gallios flow cytometer and analyzed with Kaluza-1.2 software (Beckman Coulter®). Cell-surface expression of CD107a and intracellular expression of TNF-α and IFN-γ were assessed on PBMC from the case report (in November 2010 and May 2016) or his partner (in August 2011) in the absence of target (alone), and in the presence of MHC class-I negative K562 cells or CD20 + RAJI cells treated by 1 μg/ml of anti-CD20 mAb (ocCD20; Rituximab, Roche), or an Isotype control (Ig Ctl). Effector and target are used at a 1:1 ratio. The values were analyzed with a Boolean gate algorithm (Flowjo; Tree Star). Data are presented as pie charts created with Pestle and Spice software. Colored arcs represent the frequencies of cells producing CD107a, TNF-α and IFN-γ. Pie fractions represent cells performing 0, 1, 2, or 3 functions simultaneously.

4. Results

Until May 2017, HIV-1 RNA was strictly undetectable in blood with a routine assay (<20 copies/ml) (Fig. 1b) and HIV-1 WB remained incomplete from November 2007 to April 2017 (middle panel) (Fig. 1a). Two copies of HIV-1 RNA was detected in plasma with an ultra-sensitive assay in September 2009 (detection limit <1 copy/ml), (Fig. 1b) but not in May 2015 (detection limit <1 copy/ml). Six other samples collected between February 2008 and April 2017 were assessed by ultrasensitive PCR: HIV-RNA was not detected (threshold varying between 1.1 log and 1.6 log according to the volume available) in February 2008, November 2009, September 2012, June 2013, November 2015, and April 2017. The two copies of HIV-1 RNA detected in plasma with an ultra-sensitive assay in September 2009 (detection limit <1 copy/ml) was not confirmed two month later, in November 2009 with a detection limit <8 copies/ml. In addition no HIV-RNA was detected in cerebrospinal fluid or semen in 2009 (<20 copies/ml). The patient’s CD4+ T cell count remained normal throughout follow-up (median 1230 cells/mm³, IQR, 1053-1324) (Fig. 1c).

No antiretroviral therapy was prescribed at any time during follow-up and we ruled out the possibility that the observed control of HIV-1 replication or weak reactivity of HIV-1 WB pattern were related to...
Fig. 1. Immunological and virological characteristics of the case patient (left panel) and his sexual partner (right panel), and HIV-1 phylogenetic analysis. (a) Fifteen HIV-1 WB assays were performed from November 2007 to September 2012. Eight serial samples from November 2007 to July 2008 were retested simultaneously in July 2008 (middle panel) and three samples from January 2015 to November 2015 were retested simultaneously in May 2016. The last HIV-1 WB was performed in April 2017. Dates of serological assays are indicated below the charts. (b) HIV-1 RNA was measured in blood with routine assays. The dotted line indicates the detection limit of 40 or 20 copies/ml (top panel). Ultrasensitive HIV-1 RNA assays were performed from plasma in 2009 and 2015 and HIV-DNA quantification from PBMC, rectal and ileal biopsies (bottom panel) in 2011. Two copies of HIV-1 RNA/ml were detected in 2009 (detection limit <1 copy/ml), and in 2015 (detection limit <8 copies/ml). (c) CD4+ and CD8+ T cell counts were determined in blood by flow cytometry. Dates of T-cell counts are indicated below the charts.
hidden taking of antiretroviral drugs, as no drug was detected in plasma in February 2008 and September 2013.

We detected total cell-associated HIV-DNA in PBMC collected in 2008. Cell-associated HIV-DNA was detected in PBMC at 1.1 copies/10^6 cells in 2009 and 2 copies/10^6 cells (0.4 log) in 2015. Cell-associated HIV-DNA was detected at 1.2 copies/10^6 cells in rectal but was not detected in ileal biopsies in 2011 (Fig. 1b). A 241-bp fragment of the integrase coding region (pol-IN) was amplified by PCR (Fig. 3b). Subsequent amplification attempts on the same sample and on other samples collected in 2009, with targets including highly conserved regions of the env gene (gp41), were all negative.

Finally, attempts to isolate the virus from in vitro-stimulated total and CD4 + FACS-sorted T cells from blood, bone marrow, lymph nodes and rectal biopsy specimens were negative.

Given the low HIV-1 RNA and HIV-1 DNA levels and the patient's heterozygosity for the CCR5 Δ32 haplotype, we analyzed in 2009 his CD4 + T cells' susceptibility to the following viral strains: HIVYU2b (R5-tropic), HIVNL4-3 (X4-tropic) and HIVKON, the latter being a primary isolate belonging to the same clade as his own CRF02_AG variant. Activated CD4 + T cells from blood were challenged in vitro, and p24 Gag release was monitored by ELISA. The cells were clearly susceptible to all the strains, including HIVKON (Fig. 2a).

We then analyzed extensively his immune status. The patient was HLA-A’03 - A’31 and was homozygous for the pejorative allele B’07’07 as well as for HLA-C’07 and DBQ1 06. A CD4 and CD8 T cell multi-parametric phenotypic analysis showed in 2010 and 2016 (Supplementary Table 1) normal proportions of naive (TN) and of the various memory T cell subsets (central-memory (TCM), transitional- (TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and TfH cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and (TEMRA), as well as of TfH (Follicular helper CD4 + T cells) and PD1+ memory T cell subsets (central-memory (TCM), transitional-(TTM), effector (TEM)) and terminal-differentiated effectors (TEMRA), as well as of Th1 (Follicular helper CD4 + T cells) and PD1 + Th1 cells, without increased T cell activation. The PD-1, Tim-3 and

The possibility that the case patient's CD4 + T cells expressed factors restricting HIV-1 replication was also ruled out by in vitro experiments showing his CD4 + T cells were clearly susceptible to various HIV-1 strains, including HIVKON, a primary isolate of the same clade as his own CRF02_AG variant (Fig. 2a). Thus the different outcomes of the case patient and his partner, despite infection by the same HIV strain, strongly suggest that host/genetic factors rather than viral factors were responsible.
From 2009 to 2015, no major significant difference between our case report and healthy individuals were observed. In contrast, the partner showed some functional markers which are significantly increased in HIV-1 progressors (Gumá Cabrera et al., 2006). The partner had a massive loss of capacity to producing ADCC in August 2011 (Fig. 4). Polyfunctional analysis revealed that case report and the partner are only (but strongly) different in their ability to product ADCC (Raji + anti-CD20), but not direct lysis (K562) (Fig. 4).

HIV-1 WB reactivity has previously been reported in cohorts of elite controllers (Simek et al., 2009; Canouï et al., 2017; Boufassa et al., 2011). Canouï et al. investigated an extreme HIC subset with undetectable viral load (uHIC) and no viral blips using semi-quantitative HIV-1 WB to detect IgG antibodies against HIV proteins. They found that 10 of the 47 uHICs (21%) lacked at least 1 HIV-specific antibody and were described as having weak IgG responses. Seven of these 10 uHICs lacked either anti-p68 or anti-p34 antibodies. This data further supporting the lack of recent antigenic stimulation in these patients (Canouï et al., 2017).

In the study from Pereyra et al. (2009), reactivity was detectable to multiple proteins (range 2 to 10), and the majority of individuals (77%) had a complete pattern against all the proteins tested. The most commonly detected antibodies were anti-gp120 and anti-gp160, which were detected in all individuals, followed by anti-p24, -p40 and -gp41, in
respectively 98%, 96% and 93% of individuals. The least commonly detected antibodies were those against p18, p31 and p65, which were found in respectively 80%, 84% and 86% of individuals (Pereyra et al., 2009). In the previous study, by using an ultrasensitive assay, the results showed that the number of antibodies detected correlated directly with the plasma HIV-1 RNA level, and that full WB reactivity was present in all patients with plasma viral load above 13 copies/mL. In our case report, only one on the eight samples had a VL detectable at 2 copies of HIV-1 RNA/mL of plasma (detection limit <1 copy/mL) by using an ultrasensitive PCR (Fig. 1b). His sequential patterns of the antibodies to anti-gp160, anti-gp110, anti-gp41, anti-p40, anti-p24, and anti-p18 were in accordance with the previous study, WB remaining incomplete until May 2017 (Fig. 1a). This report provided extensive longitudinal data on an EC with incomplete WB over a 10-years period.

Fig. 3. Phylogenetic analysis of IN-sequences from the case report and of Protease, Reverse Transcriptase and IN-sequences from the partner. (3a) Phylogenetic analysis of viral sequences obtained from the case patient’s PBMC DNA collected in 2008, and from plasma samples collected from his only sexual partner in June 2006 and May 2007 (HIV-1 RNA). The phylogenetic tree was constructed using 61 sequences of CRF02_AG variants available in the Los Alamos HIV sequence database (http://hiv-web.lanl.gov). The 241-bp IN coding sequences were analyzed comparatively using the MEGA analysis program (http://www.megasoftware.net) with the neighbor-joining method. Distances were calculated using the Kimura two-parameter matrix (ratio T/t = 2.0). Bootstrap analysis (500 replications) was used to test the reliability of the branching order. The tree was rooted using the sequence of the reference subtype B strain HXB2-LAI-III-BRI. The scale bar at the bottom of the figure indicates the number of base substitutions per site. (3b) HIV-1 IN-sequences from the case patient's PBMC DNA collected in February 2008 (Antoni et al., 2013), and the Protease, Reverse Transcriptase and IN-sequences from partner’s plasma samples collected in June 2006 (2a; 2b; 2c respectively) and May 2007 (3a; 3b; 3c respectively), before partner’s ARV initiation.
The extremely rare uHICs differ from HICs with blips by significantly lower ultrasensitive plasma HIV-RNA loads and HIV-DNA levels in PBMCs, higher CD4+ T-cell count at enrollment and during follow-up and with lower T-cell activation levels. In our case, the only 2 copies of HIV-1-RNA/mL of plasma detected from 2009 to 2017 (Fig. 1b) and the constantly high CD4+ T cell count above 1000/mm3 from 2007 until 2017, with, in 2017, CD4+ T-cell count higher than in 2007 (Fig. 1c), are consistent with the uHIC cohort (Boufassa et al., 2011). Our patient’s blood HIV-1 DNA reservoir appeared smaller than usually observed in ECs and in LTNPs (Fig. 1b) (Boufassa et al., 2011). This small blood HIV-1 DNA reservoir was accompanied by a very small HIV-1 DNA reservoir in gut-associated lymphoid tissue, as previously reported in several LTNP groups, including untreated patients with primary infection (Avettand-Fenoel et al., 2008). Half of the uHICs have a protective HLA allele (B*57 or *58 or *B27), weak CD8+ T-cell responses, and very small HIV-DNA reservoir (Canouï et al., 2017). The case may be one of these extreme controllers. Our case report had poly-functional HIV-1 specific CD8+ T cell responses, coproducing IFN-γ and TNF - albeit modest and fluctuating. These responses contrasted with his partner’s lack of CD8 T cell responses and were markedly higher than observed in HAART-treated non viremic patients but did not differ from those seen elsewhere in chronically viremic patients. Nevertheless they had no significant impact on HIV-1 replication in vitro.

Our case patient was HLA-A*03-A*31, B*07, with C*07 homozygous pejorative alleles (Coloccini et al., 2014) whereas his partner was HLA-B*07-B*52, C*07 heterozygous and C*12 heterozygous. Elite controllers have a variety of genetic backgrounds, although protective HLA as B*27/B*57 alleles are usually over-represented. Interestingly, the case
the 14 post-treatment controllers (PTCs) carried one HLA-B*07 allele, reported among 45% and 15% of Caucasian HIV controllers respectively versus 6.2% and 6.9%, respectively in the French Caucasian population; www.allelefrequencies.net. Neither the case report had other protective HLA alleles like HLA-B*13 (Antoni et al., 2013), B*14 (Antoni et al., 2013; Peterson et al., 2013), B*51 (Brunme et al., 2011), B*52 (Antoni et al., 2013). Our case patient and his partner shared at least one pejorative allele: the case report was homozygous for B*07, the most frequent human allele consistently linked to accelerated disease progression in B-clade, but not in C-clade infection (Klovpris et al., 2014). The influence of HLA-B*07 on the control of CRF02_AG variant being unknown to date, this allele cannot be considered as pejorative in this clinical setting. Moreover, the case report was also homozygous for the HLA-C*07 allele (Collocini et al., 2014).

Transmission of HIV-1 from a patient who developed AIDS to a patient who has maintained undetectable viral loads has already been documented (Bailey et al., 2008), but unlike our case, either both patients shared the same protective HLA-B*57 allele, or the patient who has maintained undetectable viral loads was HLA-B*57:03 (Buckheit et al., 2012). Similarly, the four patients described by Mendoza (Mendoza et al., 2012) (without any data about the partners) carried protective HLA class-I alleles, two carried an additional B*57 allele, and none carried pejorative alleles. Moroni et al. (2014) published a case of HIV-1 control in a heterosexual couple lasting >20 years, exploring the genetic background in depth. The woman possessed multiple genetic polymorphisms, including HLA alleles (B*14, B*57, C*06 and C*08:02) and HLA-C single nucleotide polymorphisms (SNPs, rs9264942 C/C and rs67384697 del/del), that have been previously individually associated with spontaneous control of plasma viremia, maintenance of high CD4(+) T cell counts and delayed disease progression. HLA-B*07 allele does not represent a true pejorative HLA class-I allele such as B35:02, (Martin and Carrington, 2013), and has been linked to disease progression with rapid seroconversion (Peterson et al., 2013). Its homozygosity for HLA-B*07-C*07, combined with the absence of a particular neutralizing activity. It is not surprising since development of a neutralizing activity requires antigenic stimulation which is only provided by a persistent level of HIV replication and HIV evolution.

The limits of our study were first that, despite we used ultrasensitive PCR for HIV-1 RNA measurement, the threshold varied between 1.1 log and 1.6 log according to the volume available. We could therefore not rule out definitively the possibility of viral blips. Secondly, we cannot exclude the possibility that the variant transmitted to the case patient harbored mutations affecting its replicative properties, as, despite using large volumes of plasma and PBMC, we could not isolate the case patient’s whole virus. When the case patient was referred in November 2007, the partner was already treated with ARV since September 2007; for ethical reasons we did not withdraw partner’s treatment to try to sequence the virus and to study the replicative capacity. Thirdly, we assessed NK cell potential by using rituximab plus Raji, but we were not able to assess the potential of serum antibodies from patients to perform ADCC function, or at least provide antibody isotypes and HIV recognition data, as there was not any plasma or serum available from our patient, and the partner moved to the provinces and was lost-to-follow-up.

A fragment of the integrase coding region (pol-IN) was amplified by PCR, but all subsequent amplification attempts, with targets including highly conserved regions of the env gene (gp41), were all negative. Phylogenetic analysis was thus performed based only on the pol-IN fragment. We suggest that such failure is due to the low virus load in the patient. In conclusion, we described an extremely prolonged and spontaneous almost complete control of HIV-1 replication in the blood and different tissues despite the lack of protective alleles. Our study may imply that the genetic background of the exposed person, the genetic background of the source, and the viral strain could interact with each other to obtain an elite controller. This case which might belong to the extremely rare subset of extreme HIV controllers with undetectable virus loads, might be taken as a model and as a creative step, in a positive direction, for future control of HIV disease (Autran et al., 2011, Autran, 2015).
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Contributors

M. Bendenoun, A. Samri, and P. Sellier conceived and wrote the study.

V. Avettand-Fenoël performed virological studies: HIV-1 RNA measurements by ultra-sensitive assay and HIV-1 DNA measurements from cells.

S. Cardinaud, B. Descours, A. Urrutia, A. Moris, G. Carcelain and V. Vieillard performed immunological studies.

M-C. Mazeron performed virological studies from plasma.

S. Brunet and F. Barin performed phylogenetic analysis.

M. Pocard and X. Dray performed the lymph nodes and GALT biopsies in the patient.

J-F. Bergmann, C. Rouzioux, F. Simon, P. Andre, and B. Autran supervised the study.

Conflicts of Interest

No conflicts of interest.

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none.

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Declaration of Interests

M. Bendenoun: received personal fees from ABBVIE, outside the submitted work; Samri: no COI.

V. Avettand-Fenoël: received grants from ViV for lecture; from Janssen for congress, outside the submitted work; S. Cardinaud: no COI.

Descours: no COI.

G. Carcelain: received personal fees from MSD France, personal fees from Gilead, personal fees from ViV healthcare, outside the submitted work; M-C. Mazeron: no COI.

J-F. Bergmann: no COI.

A. Urrutia: no COI.

F. Simon: disclosed board membership for Abbott, Beckman, bioMérieux; consultancy for Abbott, Beckman, bioMérieux, GSK, bioRad; grants for Abbott, bioMérieux, Beckman; meeting expenses: Abbott, Beckman, bioMérieux, bioRad, all outside the submitted work; P. Andre: no COI.

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V. Vieillard: no COI.

B. Autran: no COI.

F. Barin: no COI.

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References

Antoni, G., Guermon, J., Meadure, C., Samri, A., Boufassa, F., Goujard, C., et al., 2013. MHC-driven HIV-1 control on the long run is not systematically determined at early times post HIV-1 infection. AIDS 27, 1707–1716.

Autran, B., 2015. Toward a cure for HIV-seeking therapeutic vaccine strategies. Eur. J. Immunol. 45, 3215–3221.

Autran, B., Descours, B., Avettand-Fenoël, V., Rouzioux, C., 2011. Elite controllers as a model of functional cure. Curr. Opin. HIV AIDS 6, 181–187.

Avettand-Fenoël, V., Chai, M.L., Blanche, S., Burgard, M., Floc'h, C., Touré, K., et al., French Pediatric Cohort Study ANRS-CO 01 Group, 2009. LTR real-time PCR for HIV-1 DNA quantitation in blood cells for early diagnosis in infants born to seropositive mothers treated in HAART (ANRS CO 01). J. Med. Virol. 81, 217–223.

Avettand-Fenoël, V., Prazuck, T., Hoqueiloux, L., Melard, A., Michau, C., Kerdraon, R., et al., 2008. HIV-1 DNA in rectal cells is well correlated with HIV-1 DNA in blood in different groups of patients, including long-term non-progressors. AIDS 22, 1860–1862.

Bailey, J.R., O’Connell, K., Yang, H.C., Han, Y., Xu, J., Jilek, B., et al., 2008. Transmission of human immunodeficiency type virus 1 from a patient who developed AIDS to an elite suppressor. J. Virol. 82, 7395–7410.

Bashir, C., Giery, M., Charron, D., Carrington, M., 2011. HLA/KIR restraint of HIV: surviving the fitness. Annu. Rev. Immunol. 29, 295–317.

Béziat, V., Dalgarg, O., Asselah, T., Hallof, P., Bedossa, P., Boudiaf, A., et al., 2012. CMV drives clonal expansion of highly differentiated NKGC0+ NK cells expressing self-specific KIRs in patients with chronic hepatitis virus infection. Eur. J. Immunol. 42, 447–457.

Boufassa, F., Saez-Gilson, A., Len Benchmark, J., Zucman, A., Descours, B., Venet, A., et al., ANRS EPF36 HIV Controllers Study Group, 2011. CD4 dynamics over a 15-year period among HIV controllers enrolled in the ANRS French observational. PLoS One 6 (e18726).

Bouvin-Pey, M., Mordang, M., Moreau, A., Jesin, P., Simonnet, C., Tran, L., et al., 2013. Evidence for a continuous drift of the HIV-1 species towards higher resistance to neutralizing antibodies over the course of the epidemic. PLoS Pathog. 9, e1003477.

Brumme, Z.L., Li, C., Miura, T., Sela, J., Rosato, P.C., Brumme, C.J., et al., 2011. Reduced replication capacity of NL4-3 recombinant viruses encoding RT-integrate sequences from HIV-1 elite controllers. J. Acquir. Immune Defic. Syndr. 56, 100–108.

Buckheit, R.W., Allen, T.G., Alme, A., Salgado, M., O’Connell, K.A., Huculak, S., et al., 2012. Host factors dictate control of viral replication in two HIV-1 controller/chronic Progressor transmission pairs. Nat. Commun. 3, 716.

Canoud, E., Lécouroux, C., Avettand-Fenoël, V., Guoueix, M., Rouzioux, C., Saez-Girzon, A., et al., ANRS CO21 CODEX Study Group, 2017. A subset of extreme human immunodeficiency virus (hiv) controllers is characterized by a small hiv blood reservoir and a small T-cell activation level. Open Forum Infect Dis. 4 (ofx064).

Cardinaud, S., Conigliere, G., Bouzat, R., Urrutia, A., Graff-Dubois, S., Fourati, S., et al., 2011. CIL escape mediated by proteosomal destruction of an HIV-1 cryptic epitope. PLoS Pathog. 7, e1002049.

Carrington, M., Nelson, G.W., Martin, M.P., Kissner, T., Vlahov, D., Coedert, J.J., et al., 1999. HLA and HIV-1: heterozygote advantage and B ‘35-Cw04 disadvantage. Science 283, 1748–1752.

Casado, C., Colombo, S., Rauch, A., Martinez, R., Günthard, H.F., García, S., et al., 2010. Host genetic factors associated with symptomatic primary HIV infection and disease progression among different groups of patients, including long-term non-progressors. AIDS 22, 1707–1716.

Mendoza, D., Johnson, S.A., Peterson, B.A., Natarajan, V., Salgado, M., Dewar, R.L., et al., 2012. Comprehensive analysis of unique cases with extraordinary control over HIV-1 replication. Blood 119, 4645–4655.
Moroni, M., Ghezzi, S., Baroli, P., Heltai, S., De Battista, D., Pensieroso, S., et al., 2014. Spontaneous control of HIV-1 viremia in a subject with protective HLA-B plus HLA-C alleles and HLA-C associated single nucleotide polymorphisms. J. Transl. Med. 12, 335. Pereyra, F., Addo, M.M., Kaufmann, D.E., Liu, Y., Miura, T., Rathod, A., et al., 2008. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J. Infect. Dis. 197, 563–571.
Pereyra, F., Palmer, S., Miura, T., Block, B.L., Wiegand, A., Rothchild, A.C., et al., 2009. Persistent low level viremia in HIV-1 elite controllers and relationship to immunologic parameters. J. Infect. Dis. 200, 415–422.
Peterson, T.A., Kimani, J., Wachibi, C., Bielawny, T., Mendoza, L., Thavaneswaran, S., et al., 2013. HLA class I associations with rates of HIV-1 seroconversion and disease progression in the Pumwani Sex Worker Cohort. Tissue Antigens 81, 93–107.
Salgado, M., Simón, A., Sanz-Minguela, B., Rallón, N.I., López, M., Vicario, J.L., et al., 2011. An additive effect of protective host genetic factors correlates with HIV non-progression status. J. Acquir. Immune Defic. Syndr. 56, 300–305.
Samri, A., Bacchus-Souffan, C., Hocqueloux, L., Averttand-Fenoel, V., Descours, B., Theodorou, I., et al., ANRS VISCONTI Study Group, 2016. Poly-functional HIV-specific T cells in post-treatment controllers. AIDS 30, 2299–2302.
Samri, A., Durier, C., Urutia, A., Sanchez, I., Gabery-Segard, H., Imbart, S., et al., ANRS ELISpot Standardization Group, 2006. Evaluation of the inter-laboratory concordance in quantification of human immunodeficiency virus-specific T cells with a gamma interferon enzyme-linked immunospot assay. Clin. Vaccine Immunol. 13, 684–687.
Simek, M.D., Rida, W., Priddy, F.H., Pung, P., Carrow, E., Lauber, D.S., et al., 2009. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with analytical section algorithm. J. Virol. 83, 7337–7348.
Vilches, C., Castano, J., Gomez-Lozano, N., Estefana, E., 2007. Facilitation of KIR genotyping by a PCR-SSP method that amplifies short DNA fragments. Tissue Antigens 70, 415–422.
Wren, L.H., Chung, A.W., Isitman, G., Kelleher, A.D., Parsons, M.S., Amin, J., et al., ADCC study collaboration investigators, 2013. Specific antibody-dependent cellular cytotoxicity responses associated with slow progression of HIV infection. Immunology 138, 116–123.
Xie, J., Lu, W., Samri, A., Costagliola, D., Schnuriger, A., da Silva, B.C., et al., 2010. ALT-ANRS-CO15 study group. Distinct differentiation profiles of HIV-Gag and Nef-specific central memory CD8+ T cells associated with HLA-B57/5801 and virus control. AIDS 24, 2321–2329.
Yue, L., Prentice, H.A., Farmer, P., Song, W., He, D., Lakhi, S., et al., 2013. Cumulative impact of host and viral factors on HIV-1 viral-load control during early infection. J. Virol. 87, 708–715.
Zipeto, D., Beretta, A., 2012. HLA-C and HIV-1: friends or foes? Retrovirology 9, 39.