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A long-term durable remission with high-dose therapy and autologous stem cell transplant for stage IVB HIV-associated Hodgkins disease

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A 44-year-old man with relapsed HIV-associated stage IV nodular sclerosing Hodgkin's disease underwent high-dose therapy with autologous stem cell transplantation. The transplant was uncomplicated and the patient remains in complete remission at 59 months. Autologous stem cell transplantation is safe in HIV patients and can achieve long-term durable remissions in Hodgkin's disease.

A 44-year-old man was diagnosed with HIV infection in 1999. He remained well until 2 years later when the patient was diagnosed with stage IVB nodular sclerosing Hodgkin's disease with bone marrow involvement. He was initially treated with six cycles of doxorubicin, bleomycin vinblastine and dacarbazine, and achieved a complete radiological remission. Four months later he re-presented with biopsy-confirmed axillary recurrence.

At relapse, the patient received two cycles of dexamethasone, cytarabine and cisplatin as salvage chemotherapy, followed by an etoposide/granulocyte colony-stimulating factor (GCSF)-conditioned peripheral blood stem cell mobilization.

He underwent an autologous haematopoietic stem cell transplant (ASCT) in May 2002. The conditioning regimen was LACE: lomustine (cyclohexyl-chloroethyl-nitrosourea) 200 mg/m² and etoposide 1000 mg/m² on day -7, cytarabine 2000 mg/m² on days -5 and -6, and cyclophosphamide 1800 mg/m² on days -4 to -2. The stem cell dose was 4.06 × 10⁶/kg CD34 cells. Viral load at the time of transplant was 65.0 RNA copies/ml with a CD4 cell count of 479 × 10⁹ cells/l. He remained on HAART (stavudine, lamivudine and efavirenz) during the transplant procedure and received prophylactic azithromycin and septrin throughout.

The transplant procedure was uncomplicated. He developed an episode of sepsis on day 7 after transplant as a result of a coagulase-negative staphylococcal infection, which responded to intravenous antibiotics. Neutrophil engraftment occurred on day 14 and platelet engraftment on day 18. The patient was discharged home on day 20. The patient remains in complete remission at 59 months

post-ASCT. His HIV disease is well controlled, with an undetectable viral load and CD4 cell count of more than 760 × 10⁹ cells/l on HAART (efavirenz, tenofovir and lamivudine).

Information on the role of ASCT in HIV-associated lymphoma is limited. The few published small series have predominantly concentrated on patients with non-Hodgkins lymphoma (NHL). Only a few cases of ACST in HIV-associated Hodgkin's disease have been described. Krishnan *et al.* [1] described two cases of mixed cellularity Hodgkin's disease transplanted in the first relapse. Both patients entered complete remission and were reported alive in remission at 61 and 56 months. The two patients were mobilized with a cyclophosphamide/GCSF mobilizing regimen. A multi-institutional Italian study reported by Re *et al.* [2] in 2003 assessed nine out of 10 ASCT patients for HIV-related lymphoma with a short follow-up. The patients were also mobilized using cyclophosphamide with an 80% success rate. Six patients in that study remain alive at a median of 8 months. The histological subtype and length of follow-up of the four Hodgkin's disease patients transplanted were unclear in the final analysis, which did not differentiate between Hodgkin's disease and NHL. More recently, the European Group for Blood and Marrow Transplant Lymphoma Working Party have published in abstract form a series of 44 HIV-associated lymphomas with 23% Hodgkin's disease with a median follow-up of 36.3 months [3]. The overall survival (NHL and Hodgkin's disease) for those with chemosensitive disease in first complete remission at the time of ASCT was 85%. Currently no data are available on the specific outcome of the cases of Hodgkin's disease.

Here, we report that a LACE-conditioned ASCT for HIV-associated Hodgkin's disease can result in long-term complete remission. ASCT is capable of achieving long-term complete remission in HIV nodular sclerosing Hodgkin's disease (intermediate prognosis) as well as in mixed cellularity Hodgkin's disease. Etoposide/GCSF can achieve an adequate cell harvest dose and can be used as an alternative to cyclophosphamide/GCSF to mobilize peripheral blood stem cells with the concurrent use of antiretroviral agents. This information adds to the slowly emerging data on ASCT in HIV. We concur with the other investigators that durable remissions are achievable in this setting, and that in well-controlled patients HIV status is no barrier to high-dose therapy. HIV infection has, in the era of HAART, become for many sufferers a chronic condition, often managed in the outpatient setting with increased long-term survival.

More information is required; however, it is becoming increasingly evident that ASCT results in an improved survival much in the way that it does in the non-HIV setting. We believe that transplant centres currently need to collaborate to review data collectively on ASCT in HIV-associated Hodgkin's disease to try to achieve a greater understanding of the role of ASCT in this setting.

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HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz

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HLA typing, demographic and immunological risk factors for nevirapine and efavirenz reactions were studied in a French cohort of HIV patients. Cases with isolated rash were significantly associated with HLA-DRB1*01 allele. No liver toxicity was observed and no association was detected with the percentage of CD4 T-cells. This study suggests that HLA-DRB1*01 allele plays an important role in susceptibility to cutaneous reactions associated with nevirapine and efavirenz in HIV patients.

Nevirapine (NVP) and efavirenz (EFV) are non-nucleoside reverse transcriptase inhibitors commonly used in the treatment of HIV-1-infected patients. Although 20–35% of patients receiving NVP treatment develop cutaneous

adverse reactions [1,2], 32% of patients develop a rash when treated with EFV [3]. In both cases, the development of hypersensitive reactions occurs within 6 weeks of treatment initiation [4].

Increasing evidence shows that drug hypersensitive reactions are genetically determined. Genetic screenings of human leukocyte antigen (HLA) markers (located within the class I and class II regions of the major histocompatibility complex) have demonstrated the involvement of genetic factors in the susceptibility to hypersensitive reactions to abacavir [5] and NVP [6]. Recently, hepatotoxic/multisystem NVP reactions (defined by serum alanine aminotransferase levels five-fold greater or more than the upper normal limit) were associated with two risk factors: *HLA-DRB1*0101* and CD4 status. Higher pretreatment CD4 T-cell counts ($\geq 25\%$) and *HLA-DRB1*0101* were associated with an increased risk of developing these reactions [6]. By contrast, neither *HLA-DRB1*0101*, nor the percentage of CD4 T cells alone were associated with NVP-induced rash [6]. However, evidence that the mechanism of NVP-induced rash is immune-mediated was provided in an animal model [7].

We explored the association between *HLA-DRB1* alleles and EFV/NVP hypersensitivity in an HIV French Caucasian cohort with skin rash. At the same time, patient immunological characteristics were also evaluated for any possible role in EFV/NVP hypersensitive reactions.

From 2002 to 2004, 21 HIV-infected Caucasian patients (aged > 18 years) were prospectively enrolled in the study. Patients were recruited from nine hospitals in France, according to French laws governing participation in biomedical research and with the approval of the local Ethics Committee. In accordance with the principles of the Helsinki Declaration, each participant received information about the study and provided their informed consent. Patient data protection and confidentiality were ensured.

Among the 21 patients, seven and 14 subjects were treated with EFV and NVP, respectively. Six of the 21 individuals had developed cutaneous adverse drug reactions (hypersensitive group). The control group (15 individuals) had received antiretroviral treatment for at least 6 months without any evidence of cutaneous adverse reactions (tolerant group).

All patients and controls were typed for the *HLA-DRB1* locus. Low resolution *HLA-DRB1* genotyping was performed by the polymerase chain reaction (PCR) with sequence-specific primers (OLERUP SSP HLA-DRB1 kit; GenoVision, Vienna, Austria). After migration of PCR products on 2% agarose gels, *HLA-DRB1* allele types were determined with HELMBERG-SCORE software (GenoVision).

Table 1. Demographics and immunological variables in the hypersensitive and tolerant group.

Variable	Hypersensitive (n = 6)	Tolerant (n = 15)	P-value
Age, mean $\pm$ SD (years)	50 $\pm$ 10	44 $\pm$ 11	0.22
Sex, n (%)			0.93
Male	5 (83)	11 (73)	
Female	1 (17)	4 (27)	
Plasma HIV-1 RNA			
$\times 10^3$ copies/ml (mean $\pm$ SD)	48 $\pm$ 112	13 $\pm$ 33	0.49
> 200 copies/ml, n (%)	4 (67)	4 (27)	0.15
CD4 T-cell count			
$\times$ cells/ μ l (mean $\pm$ SD)	432 $\pm$ 233	541 $\pm$ 229	0.36
CD4 cells $\geq$ 25%, n (%)	1 (17)	7 (47)	0.33

The two groups of NVP/EFV hypersensitive and tolerant patients were compared for age, sex, CD4 T-cell count and HIV viral load. Demographic (sex, age), and immunological data (CD4 T-cell count and HIV viral load) were tested using Fisher's exact tests for categorical data and *t*-tests for continuous data. The HLA typing was analysed using a logistic regression model. $P < 0.05$ was considered statistically significant. The corrected P -values (P_c) were adjusted using Bonferroni's correction for comparison of multiple alleles (11 observed alleles for the *HLA-DRB1* locus). All statistical analysis were performed using R statistical software (<http://www.r-project.org/>).

None of the considered variables was significantly associated with hypersensitive reactions (Table 1). All the patients with NVP/EFV hypersensitivity developed isolated skin rash and none showed liver toxicity. Eighty-three percent (five of six) of the NVP/EFV hypersensitive subjects had the *HLA-DRB1*01* allele compared to 7% (one of 15) in the tolerant group ($P = 0.004$, $P_c = 0.04$). The *HLA-DRB1*01* allele, present in 14% of the study cohort, was associated with isolated rash.

No significant differences in the risk of isolated rash were found between the NVP/EFV-hypersensitive and tolerant groups stratified by the percentage of CD4 T cells ($\geq 25\%$ and $< 25\%$). These results are in agreement with the data presented for isolated rash by Martin *et al.* [6] in which no association was detected with the percentage of CD4 T cells.

The results of our study suggest that the mechanism of NVP/EFV-related isolated rash is different from the mechanism in cases with hepatic/systemic reactions. The isolated rash risk appears to depend on the presence of the predisposing allele *HLA-DRB1*01* alone, whereas the risk of hepatic/systemic reactions is associated with an interaction between genetic and immunological factors. Further studies characterizing the NVP/EFV-associated reactions (e.g. hepatotoxicity, fever and/or rash) with larger cohorts are needed. New studies should allow the identification of the underlying risk factors. This would

lead to the development of a diagnostic test, and help decrease or eliminate the incidence of NVP/EFV hypersensitive reactions.

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The role of protective HCP5 and HLA-C associated polymorphisms in the control of HIV-1 replication in a subset of elite suppressors

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Elite suppressors (ES) are untreated HIV-1-infected patients who maintain undetectable viral loads. A recent whole-genome analysis identified two independent polymorphisms associated with low viral

loads in untreated HIV-1 infection. We screened 16 ES; none were positive for the protective HLA complex 5 gene polymorphism, and only four were positive for the protective polymorphism associated with the HLA-C gene. These results suggest that some ES control viremia by mechanisms independent of the newly-identified genetic factors.

The mechanisms by which elite suppressors (ES) control viral replication remain unclear. Although several studies [1,2] have shown that some may be infected with a defective virus, we recently demonstrated that some ES are infected with a fully replication-competent virus [3]. This strongly suggests that host factors play a role in the control of viral replication. The HLA-B*57 and HLA-B*27 [4–7] alleles are over-represented among ES, which has been interpreted as evidence for a role of CD8+ T cells in the control of viremia. Support for this hypothesis came from multiple studies showing that HIV-1-specific CD8+ T cells from ES were qualitatively superior to those from patients with progressive disease [8–13].

However, a recent genome-wide screen has identified single nucleotide polymorphisms (SNP) in two genes that are associated with low viral loads in untreated patients [14]. The protective SNP in one of the genes, HLA complex P5 (HCP5), is in strong linkage disequilibrium with the HLA-B*5701 allele [14]. It is thus possible that the HCP5 polymorphism and not HLA-B*5701 plays a direct role in the control of viremia, and that the qualitatively superior HLA-B*57-restricted CD8+ T cell

functions observed in ES are a result, rather than a cause, of the control of viral replication. On the other hand, the other protective polymorphism, associated with the HLA-C gene [14], may control expression levels of HLA-C proteins and thus enhance presentation of HIV-1-specific antigens. To determine the role of these polymorphisms in the control of HIV-1 replication in ES, we performed genotypic analysis on peripheral blood mononuclear cells from 19 patients.

The target SNPs were amplified from genomic DNA by polymerase chain reaction (PCR) reactions using locus-specific primers. The primers used for detecting the HCP SNP were HCP5-F1: TAC CCT CAT TGT GTG ACA GCA, and HCP5-R1: GTC GTG GGATTT TGC ACT TC. The primers used for detecting the HLA-C associated SNP were HLA-C-F2: AGG GTG GTG CCA AGTATG AG, and HLA-C-R2: CTT CTA GAG CCC CGT GGA G. The PCR conditions used included denaturation at 94 °C for 3 min, followed by 30 cycles of 94 °C for 30 s, 60 °C for 30 s, and 68 °C for 30 s. Polymorphisms were detected by sequence analysis of gel-purified PCR products (Qiagen, Valencia, California, USA). All heterozygous SNPs were confirmed by cloning.

As shown in the Table 1, nine ES were positive for the HLA-B*5703 allele and one was HLA-B*5702-positive. Both alleles are closely related to HLA-B*5701, which was found to be in strong linkage disequilibrium with the protective HCP5 SNP. It is thus surprising that none of the HLA-B*5702/5703 ES were positive for the protective HCP5 allele. By contrast, the protective allele was present in an HLA-B*5701 patient with a low but detectable viral load and an HLA-B*5701 patient with

Table 1. Clinical characteristics and single nucleotide polymorphism (SNP) genotypes of elite suppressors (ES), low level viremia patients (LV) and patients with progressive disease (P).

	Year of diagnosis	Last CD4+ T cell count (cells/ μ l)	HIV-1 RNA (copies/ml)	Race	HLA-A alleles	HLA-B	HCP5 SNP	HLA-C SNP
ES1	1999	827	< 50	AA/C	24,26	14,27	T/T	C/C
ES2	1986	399	< 50	AA	02,31	5703,44	T/T	T/T
ES3	1991	728	< 50	AA	25,68	5702,51	T/T	T/T
ES4	1996	783	< 50	AA	02,30	08,44	T/T	T/T
ES5	1990	839	< 50	AA	23,68	5703,58	T/T	C/T
ES6	1992	965	< 50	AA	23	5703,15	T/T	T/T
ES7	1994	1362	< 50	AA	30,32	5703,81	T/T	T/T
ES8	2003	602	< 50	AA	02,03	5703,44	T/T	T/T
ES10	2002	900	< 50	C	24,31	44,51	T/T	T/T
ES12	2004	1080	< 50	AA	02	5703,53	T/T	T/T
ES13	1993	721	< 50	AA	02,23	35,63	T/T	T/T
ES14	2002	939	< 50	AA	03,33	52,78	T/T	T/T
ES15	1996	927	< 50	AA	30,55	5703,07	T/T	C/T
ES17	1999	1050	< 50	C	01,11	08,27	T/T	C/T
ES18	1998	1330	< 50	AA	23,74	5703,42	T/T	T/T
ES19	1996	732	< 50	AA	01,30	5703,07	T/T	T/T
LV1	2006	651	84	C	03,26	5701,15	G/T	C/T
P1	1988	241	62 272	AA	02/92 ^a ,11	5701,35	G/T	
P2	2002	845	13 870	AA	31,66	5703,44	T/T	T/T

Protective SNPs are shown in bold. AA, African-American; C, Caucasian.

^aAllele is either A*02 or A*92.

progressive disease. One of 16 ES was homozygous and three others were heterozygous for the protective HLA-C-associated SNP. This allele has a relatively high frequency in Sub-Saharan Africans and thus would be expected to be relatively common in our African-American cohort of patients. A chi-square analysis showed that the observed frequency in our patients of African descent who are homozygous (0.07) and heterozygous (0.143) for the protective SNP is not significantly different from that expected based on the frequencies observed in a cohort of Sub-Saharan African patients (0.07 and 0.368, respectively) in the NCBI database ($q = 0.48$). This is not a perfect analysis because African-American patients may have significant genetic differences from Sub-Saharan Africans and, although these data need to be confirmed in a larger cohort of ES, the preliminary data suggest that the protective allele cannot explain the control of viremia in the majority of our patients.

It is interesting that 12 of the 16 patients controlled viral replication without having either of the two protective SNPs with the highest impact on viral load in untreated patients. In addition, three of four patients (ES4, ES8 and ES10) from whom we have isolated replication-competent virus in the past [3] were negative for both protective alleles. Thus, there are clearly some patients who are able to control pathogenic HIV-1 without HCP5 or the HLA-C associated polymorphisms.

It is unclear why none of our HLA-B*5703-positive ES expressed the protective HCP5 allele. The frequency of this allele in the NCBI database is very low in Sub-Saharan Africans and thus would also be expected to be also low in our cohort, which is predominantly comprised of patients of African descent. Of note, one African-American HLA-B*5701+ patient with progressive disease was positive for this HCP5 protective allele. Further analysis is warranted to determine whether the lack of the protective HCP5 allele in our cohort is due to the predominance of African-American patients or the lack of HLA-B*5701 patients. There may also be other genes in linkage disequilibrium with HLA-B*5703 that play a major role in the control of viral replication in these patients. It will thus be important to perform genome-wide analyses in cohorts of patients of African descent.

The clinical history of Progressor # 2 (P2) has features that argue both for and against a role for genetic factors other than HLA-B*57 in the control of viral replication. This HLA-B*5703 patient, who has neither the HCP5- or HLA-C-associated protective SNPs, completely controlled a pathogenic CXCR4-tropic HIV-1 isolate shortly after primary infection [15]. This control may have occurred before an adaptive cellular immune response could have developed. Furthermore, the low frequency of latently infected cells observed shortly after seroconversion suggests that he never had high levels of

viremia [15]. This is consistent with a strong initial innate immune response. However, he experienced a virologic breakthrough 12 months after seroconversion. Full viral genome sequencing before and after viremia revealed only changes in two HLA-B*57-restricted CD8+ T cell epitopes, reversions of the M184V drug resistance mutation and a novel Vpu mutation. The M184V reversion was not accompanied by a major increase in viral fitness, so it is unclear how any of these mutations would affect an innate response. On the other hand, the temporal relationship between the development of the escape mutations and virologic breakthrough strongly suggests a role of the adaptive immune response in the control of viremia. Further studies will be needed to determine how much of a role other genetic factors play in the control of viral replication in HLA-B*5703-positive ES.

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