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Hot News

HIV Tropism Shift: New Paradigm on Cell Therapy Strategies for HIV Cure

CCR5 and CXCR4 are the main cellular coreceptors involved in the entry of HIV-1 into the host cells. Certain individuals possess a 32 base pair deletion in the CCR5 allele *(CCR5 delta32),* which produces a truncated form of this coreceptor associated with a natural resistance to HIV infection when this appears in homozygosis. These findings have inspired the design of anti-HIV drugs, such as the CCR5 antagonists (i.e. maraviroc), which block the interaction between the virus and the CCR5 coreceptor inhibiting viral entry.

Gene therapy approaches to downregulate or eliminate the expression of CCR5 on the host cells are also being evaluated. Such strategies raised greater scientific interest with the first case reported of HIV cure in a patient who received hematopoietic stem cell transplantation from a homozygous *CCR5 delta32* donor as part of his treatment for acute myeloid leukemia (Hütter, et al. N Engl J Med. 2009;360:692-8). This case, known as the "Berlin patient", although it remains unique, has opened new prospects and has shed light on HIV eradication.

Nonetheless, several clinical and technical challenges (i.e. HIV reservoirs, stem cell sources, HLA donor/recipient compatibility) must be overcome before overestimating the use of stem cell transplantation strategies for HIV cure, as recently shown hereby (Kordelas, et al. N Engl J Med. 2014;371:880-2). This study describes the outcome in a HIV-infected patient with anaplastic large-cell lymphoma who underwent stem cell transplantation from a homozygous *CCR5 delta32* donor.

Before transplantation, HIV tropism for the chemokine coreceptor (CCR5 or CXCR4) was determined genotypically using the geno2pheno algorithm. The viral tropism from viral RNA was predicted as R5 (false positive rate [FPR]: 24.7%), but there was evidence of the presence of X4-tropic strains when HIV tropism was determined from proviral DNA (FPR: 6.6%) following the European Recommendations for HIV tropism interpretation (classified as R5 tropic if FPR > 10%) (Vandekerckhove, et al. Lancet Infect Dis. 2011;11:394-407). During the transplantation procedure, antiretroviral therapy (ART) was discontinued but restarted three weeks after because of a HIV RNA rebound of > 90,000 copies/ml. During the viral rebound, HIV tropism was predicted as X4 (FPR: 0.4%). The reintroduction of ART effectively suppressed viral replication, but the patient had a relapse of T-cell lymphoma and ART was again stopped, leading to a second viral load rebound, and he died shortly after.

The HIV tropism analysis in this patient showed a shift from a dominant R5 tropic HIV population before transplantation towards X4 tropic after that. This shift was probably driven by the presence of stem cell homozygosis for the *CCR5 delta32* polymorphism that might favor the viral evolution towards an X4 tropism and leading the infection of new cells through the CXCR4 coreceptor.

This case highlights a new paradigm for stem cell transplantation strategies from *CCR5 delta32* homozygosis donors for HIV eradication. Moreover, it suggests HIV tropism monitoring to evaluate the relevance of changes in the coreceptor use from R5 to X4 tropic as a potential mechanism of viral escape in CCR5-knockout approaches looking for HIV cure.

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Prioritization of New Oral Hepatitis C Therapies for HIV Patients

Access to antiretroviral therapy prevents progression of immunodeficiency and development of opportunistic cancers and infections in HIV-infected persons. However, the virus cannot be eliminated and lifelong HIV treatment is needed. For this reason, tolerance and side effects have become an important consideration when choosing HIV drugs. Integrase inhibitors (i.e. dolutegravir) and nonnucleoside analogues (i.e. rilpivirine) are the preferred third agents to be used along with a nucleos(t)ide analogue backbone, either abacavir/lamivudine or tenofovir/emtricitabine. Single-tablet regimens with three agents are currently available and significantly improve HIV treatment adherence. In contrast, HIV protease inhibitors are now preferred only for treatment failures, given their greater resistance barrier but increased potential for drug interactions and metabolic complications, including dyslipidemia, insulin resistance and overall higher cardiovascular risk.

The current situation for hepatitis C is dramatically different. The recent development of direct acting

Table 1. Current recommended DDA combinations

HCV genotype	Preferred	Alternate
G1	Sofosbuvir + Ledipasvir Sofosbuvir + Simeprevir	Sofosbuvir + Daclatasvir Paritaprevir/r + Ombitasvir + Dasabuvir
G2	Sofosbuvir + Ribavirin	Sofosbuvir + Ledipasvir
G3	Sofosbuvir + Daclatasvir	
G4	Sofosbuvir + Ledipasvir Sofosbuvir + Simeprevir	Sofosbuvir + Daclatasvir
G5, G6	Sofosbuvir + Ledipasvir	Sofosbuvir + Daclatasvir

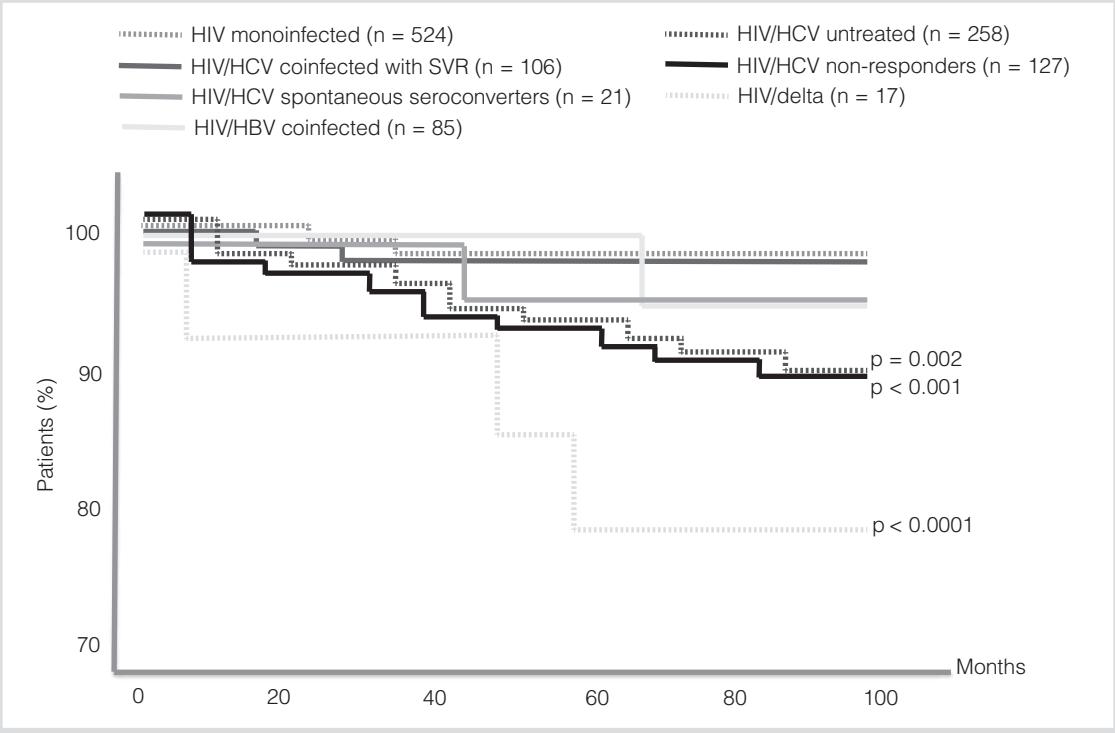

Figure 1. *Time free from liver decompensation events or death in 1,147 HIV-infected patients.*

antivirals (DAA) against HCV has revolutionized the field. The virus can be eradicated from most chronic hepatitis C patients with short courses (generally 8-12 weeks) of DAA combinations. The selection of the most convenient DAA regimen is firstly driven by HCV genotype, as shown in table 1. However, adding ribavirin and/or longer treatment duration may be considered for patients with advanced cirrhosis, prior null response and/or very high viral load.

Following the approval of the first DAAs, major attention has increasingly been focused on special patient populations, including HIV/HCV coinfected individuals. We know now that coinfected patients exhibit the same cure rates of over 90% with interferon-free oral DAA combinations than HCV-monoinfected individuals (Sulkowski, et al. JAMA. 2014;312:353-61). Accordingly, current guidelines for hepatitis C therapy no longer separate mono- and coinfected subjects.

However, indications for HCV therapy and DAA drug selection may differ in distinct patient groups. There are two special considerations for HIV/HCV

coinfected patients. First, the need to check for drug-drug interactions between antiretrovirals and HCV drugs, especially HIV and HCV protease inhibitors that exhibit a high risk of clinically significant drug interactions. Secondly, because of the faster progression of liver fibrosis and the greater risk of hepatic decompensation in HIV/HCV coinfected patients, even when HIV suppression and good CD4 counts are achieved with antiretroviral therapy (Lo Re, et al. Ann Intern Med. 2014;160:369-79), modern HCV treatments need to be prioritized and generally offered to all coinfected patients. Otherwise premature death would prevail in HIV/HCV coinfected vs. HIV-monoinfected patients, as shown in figure 1 that represents survival outcomes in a large cohort of HIV patients followed during the last decade (Fernandez-Montero, et al. Clin Infect Dis. 2014;58:1549-53).

Besides the specific benefit on the liver, there is a wide range of extrahepatic gains that follow therapeutic HCV eradication, taking off the damage resulting from systemic inflammatory phenomena and immune activation associated with persistent HCV replication (Lee, et al. J Infect Dis. 2012;206:469-77). Ultimately, clearing HCV as soon as possible in HIV/HCV coinfected patients may restore the natural history of successfully treated HIV infection, which is currently similar to that of the general population (Lewden, et al. Int J Epidemiol. 2012;41:433-45).

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