Title	Identification of potential drug resistant mutations in HIV-1 infected patients with long-term undetectable viral load after receiving HAART
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N423K in the C4 region of gp120 was necessary for utilizing inhibitor-bound CCR5 receptor while the other gp120 mutations (R117Q, KG138-39ΔΔ, L396V) augmented resistance levels. Resistance to MVC and other CCR5 antagonists is typically associated with a variety of gp120 mutations but almost all are linked to mutations in the V3 loop, *i.e.* necessary for the resistant phenotype. In our MVC resistance selection experiments, a mutation at the tip of the V3 loop emerged in both untreated and MVC treated viral passages. This Q315R mutation was not associated with altered MVC sensitivity. Receptor affinity profiling using 293 Affinofile cells revealed an overall reduction in entry efficiency with the development of resistance.

CONCLUSIONS: The development of resistance to maraviroc in a subtype A primary HIV-1 isolate resulted in multiple mutations throughout gp120 but was primarily linked to a novel N423K mutation in C4 region. Resistance related to the ability to utilize an inhibitor-bound receptor for viral entry. Unlike all previous studies, resistance to MVC was not associated with a change in the V3 loop, *i.e.* a region responsible for engagement with CCR5. Models of X-ray crystal structures suggest resistance mutations are in approximation to the CCR5 binding site in gp120.

ABSTRACT 40

Identification of Potential Drug Resistant Mutations in HIV-1 Infected Patients with Long-term Undetectable Viral Load after Receiving HAART

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BACKGROUND: This study aimed to identify potential drug resistant mutations in proviral DNA in HIV patients with long-term undetectable viral load after receiving HAART.

METHOD: Peripheral blood mononuclear cells (PBMC) were collected from 45 patients twice per year from 2005 to 2009. These patients have been receiving effective highly active antiretroviral therapy (HAART) for 3 to 13 years. The env gene (C2V5), protease (PR) gene and the first 400 codons of the reverse transcriptase (RT) gene were amplified from PBMC DNA, sequenced and subjected to phylogenetic analysis.

RESUTS: A total of 190 sequences of PR and RT and 37 sequences of C2V5 region of env gene were amplified from PBMC samples of the patients. C2V5 amplification failed in 8 patients, while PR and RT amplification failed in 7 patients. According to sequencing results of C2V5 or PR and RT genes, 29 (70.7%) patients were infected by HIV-1 AE subtype, 8 (19.6%), 3 (7.3%) and 1(2.4%) patients were infected by B and C and CRF08_BC subtypes, respectively. Thymidine analog mutation (TAM) type II pattern selected by the thymidine analogs was detected in 5 patients who have received antiretroviral therapy for about 10 years. Two of these 5 patients also developed multi-nucleoside resistance mutation Q151M and M184I, respectively. The most common NRTI resistance mutation, M184V, was found in two patients, including one who developed major protease inhibitor resistance mutation L90M. No any drug-resistant mutation was found in the other 14 patients who have received CBV-based or 3TC/ABC based treatment for 3 to 12 years. Phylogenetic analysis showed short genetic distances in different time points during treatment.

CONCLUSIONS: TAM type II pattern mutations can persist in provial DNA for longer than 10 years. The possibility of developing major resistant mutations is low and proviral DNA evolution is limited in patients with successful HAART.