

Mutations Based on Viral Decay Acceleration in the HIV-1 Genomes of a Clinical Population Treated with the Mutagenic Nucleoside KP1461

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Abstract

The deoxycytidine analog KP1212, and its prodrug KP1461, are prototypes of a new class of antiretroviral drugs designed to increase viral mutation rates, with the goal of eventually causing the collapse of the viral population. KP1212 has been shown to diminish or extinguish HIV-1 replication in cell culture, and, in a phase I clinical trial, had a very good safety profile. Here we present an extensive analysis of viral sequences from patients from the first “mechanism validation” phase II clinical trial in which “salvage” patients received 1600 mg of drug twice per day for 124 days. The Phase IIa study did not demonstrate significant diminution of viral load over the course of study. This was not unexpected as prior cell culture studies showed little change in viral titer prior to population collapse. Thus, in the present work we sought to determine whether there was a subclinical impact of KP1461 therapy. Given that the proposed mechanism of action of KP1212 results in viral mutation, we performed gene sequencing of a very large number (>100) of sequences derived from individual HIV-1 RNA templates, after 0, 56 and 124 days of therapy from 10 treated and 10 untreated individuals. Private mutations, those not found in multiple viruses, were similar in treated and control individuals at day 0 ($p=0.28$), but were increased in treated individuals after 56 ($p=0.02$) and 124 ($p=0.001$) days of drug treatment. Furthermore, the spectrum of mutations observed in the treated group was distinct from that of the controls, with an excess of A to G and G to A mutations ($p=0.01$), and to a lesser extent T to C and C to T mutations ($p=0.09$), in the treated group, as predicted by the mechanism of action of the drug (transition mutations with a bias toward A/G mutations). We also report analyses of KP1212 in solution and demonstrate the presence of the predicted tautomeric forms that would result in mispairing of the analog during DNA syntheses. The observed increase in mutations in treated patients and the chemical properties of the new drug support a new mechanism of action by a novel antiretroviral therapy in humans.