

18th International HIV Drug Resistance Workshop



Basic Principles & Clinical Implications

June 9–13 2009, Fort Myers, Florida, USA

MECHANISMS ASSOCIATED WITH HIV-1 RESISTANCE TO ACYCLOVIR BY THE V75I MUTATION IN REVERSE TRANSCRIPTASE

Antivir Ther 2009; 14 Suppl 1:A21 (abstract no. 19)

EP Tchesnokov¹, A Obikhod², I Massud², A Lisco³, C Vanpouille³, B Brichacek³, J Balzarini⁴, C McGuigan⁵, M Derudas⁵, L Margolis³, RF Schinazi² and M Götte¹

¹McGill University, Montreal, QC, Canada; ²Emory University School of Medicine and Veterans Affairs Medical Research, Atlanta, GA, USA; ³National Institutes of Health, Bethesda, MD, USA; ⁴Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium; ⁵Welsh School of Pharmacy, Cardiff University, Cardiff, UK

BACKGROUND: It has recently been demonstrated that the antiherpetic drug acyclovir (ACV) also displays antiviral activity against the human immunodeficiency virus type-1 (HIV-1). The triphosphate form of ACV is accepted by HIV-1 reverse transcriptase (RT) and subsequent incorporation leads to classical chain termination. As demonstrated for all approved nucleoside analogue RT inhibitors (NRTIs), the selective pressure of ACV can cause the emergence of resistance. V75I, M184V and T69N have been identified in cell-based selection experiments, and the V75I mutation in HIV-1 RT appears to be dominant in this regard. By itself, this mutation is usually not associated with resistance to currently approved NRTIs. Here, we studied the underlying biochemical mechanism.

METHODS: We used a variety of biochemical approaches, including enzyme kinetics, binding studies and high-resolution footprinting experiments to elucidate the molecular basis for ACV resistance.

RESULTS: We demonstrate that V75I is also selected under the selective pressure of a monophosphorylated prodrug that was designed to bypass the bottleneck in drug activation to the triphosphate form (ACV-TP). Pre-steady-state kinetics reveal that V75I discriminates against the inhibitor at the level of catalysis, while binding of the inhibitor remains largely unaffected. The selective advantage for the natural nucleotide over the inhibitor, observed with WT RT, is 10-fold increased with the V75I mutant. Moreover, the incorporated ACV-monophosphate (ACV-MP) is vulnerable to excision

in the presence of the pyrophosphate (PPi) donor ATP. V75I compromises binding of the next nucleotide that can otherwise provide a certain degree of protection from excision through dead-end-complex formation.

CONCLUSIONS: The results of this study suggest that ACV is vulnerable to two different resistance pathways. Discrimination against the inhibitor at the level of incorporation appears to be the dominant mechanism. Changes at position V75 can affect the precise positioning of amino acids Q151 and/or R71 that are directly involved in the catalytic step. Together, these findings warrant further investigation with respect to the detailed resistance profile of ACV to better assess its potential clinical utility in combination with established antiretrovirals.

2009-06-09

19

Copyright © 2009 - [International Medical Press Ltd.](#). Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.