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PharmGKB summary: zidovudine pathway

Yogita Ghodke^a, Peter L. Anderson^c, Katrin Sangkuhl^d, Jatinder Lamba^{a,b}, Russ B. Altman^{d,e}, and Teri E. Klein^d

^aDepartment of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, Minnesota

^bPUMA Institute of Personalized Medicine, University of Minnesota, Minneapolis, Minnesota

^cDepartment of Pharmaceutical Sciences, University of Colorado, Aurora, Colorado

^dDepartment of Genetics, Stanford University, Stanford, California, USA

^eDepartment of Bioengineering, Stanford University, Stanford, California, USA

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Introduction

Zidovudine (ZDV), also known as azidothymidine (other names AZT; Aztec; Novo-Azt; Retrovir), is an important drug used for the treatment of HIV infection. It is a prodrug that needs to be activated by phosphorylation, and belongs to the family of nucleoside analog reverse transcriptase inhibitors (NRTIs) and is structurally related to the endogenous nucleoside thymidine with an azido group in place of the hydroxyl group at the 3' position of the deoxyribose ring. The presence of azido group prevents the formation of phosphodiester linkages required for DNA replication, causing chain termination. This is the mechanism by which ZDV interferes with viral replication. The effectiveness of ZDV in the treatment of HIV infection is because of its selective affinity for HIV reverse transcriptase as opposed to human DNA polymerases.

Pharmacokinetics

The anti-HIV drug ZDV (3-azido-2',3'-dideoxythymidine) has three important pathways of clearance.

ZDV is a prodrug and must be activated by phosphorylation in lymphocytes to exert its antiviral action. However, in quantitative terms, this is a minor pathway, probably accounting for less than 1% of the overall clearance. ZDV passes through membranes by passive diffusion or through uptake transporters such as solute carrier family 28 (sodium-coupled nucleoside transporter), member 1 (SLC28A1) and member 3 (SLC28A3), solute carrier family 22 (organic anion transporter), member 6 (SLC22A6), member 7 (SLC22A7), member 8 (SLC22A8), and member 11 (SLC22A11) [1–3]. ZDV is readily transferred from

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Correspondence to Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, 300 Pasteur Dr. Lane L301, Mail Code 5120, Stanford, 94305-5120 California, USA, Tel: +1 650 725 0659; fax: +1 650 725 3863; feedback@pharmgkb.org.

Conflicts of interest

Dr Anderson receives donated study drug from Gilead Sciences. For the remaining authors there are no conflicts to interest.

the apical to the basal compartment by SLC28A3. SLC28A1 is also able to translocate antiviral nucleoside derivatives such as ZDV. SLC22A6, SLC22A7, SLC22A8, and SLC22A11 mediate renal ZDV transport [2,4–6]. ZDV undergoes intracellular phosphorylation through three cellular kinases. Thymidine kinase (primarily 1) is responsible for the conversion of ZDV into ZDV-monophosphate, which in turn is converted into ZDV diphosphate through thymidylate kinase, which is the rate-limiting step. The conversion of ZDV diphosphate into the active triphosphate metabolite (ZDV-TP) is mediated by the enzyme nucleoside-diphosphate kinase [7,8].

The second metabolic pathway involves inactivation of ZDV by glucuronidation, resulting in the formation of 3'-azido-3'-deoxy-5'-D-glucopyranuronosylthymidine [5'-glucuronyl zidovudine (GZDV)]. GZDV is inactive, and ~60–70% of the drug is excreted in urine in the form of glucuronide [8], thus indicating that glucuronidation is the predominant pathway in the metabolism of ZDV. Of 11 different UDP glucuronosyltransferases screened, UDP glucuronosyltransferase 2 family, polypeptide B7 (UGT2B7), has been identified as the principal isoform responsible for ZDV glucuronidation [8–10] (Fig. 1).

The third metabolic pathway involves reduction of the azido moiety, resulting in the formation of 3'-amino-3'-deoxythymidine (AMT). Cytochrome P450s and P450 reductase have been implicated in the formation of AMT [8,11–13]. The formation of AMT metabolite has been observed in both rat and human liver microsomes [12]. AMT has been shown to be approximately five-fold to seven-fold more toxic to human hematopoietic progenitor cells, contributing toward the cytotoxicity of ZDV in patients.

Renal clearance is an important elimination pathway for antiviral agents and is controlled mostly by membrane transport proteins. Fourteen percent of the parent compound and ~74% of the glucuronide form have been recovered in the urine sampled [14].

Transporters belonging to the ABC family, namely the ATP-binding cassette, subfamily B (MDR/TAP), member 1 (ABCB1), ATP-binding cassette, subfamily C (CFTR/MRP), member 4 (ABCC4) and member 5 (ABCC5), and ATP-binding cassette, subfamily G, member 2 (ABCG2), have been implicated in the clearance of ZDV [2,15–20]. ABCG2 is a cellular factor that modulates the anti-HIV-1 activity of NRTIs. The ABC transporter family members, multidrug resistant-1 (MDR-1), and multidrug resistance-associated proteins (MRPs) can efflux both NRTIs and NRTI-monophosphates from intracellular compartments. ZDV increases the expression of multidrug transporters, thereby decreasing its own pharmacological activity [2,15–20].

Pharmacodynamics

In viral-infected cells, a pharmacologically active form of ZDV, ZDV-TP, inhibits the activity of HIV-1 reverse transcriptase by competing with its natural nucleotide counterpart thymidine triphosphate for incorporation into newly synthesized viral DNA. Once incorporated, it leads to DNA chain termination and stops further DNA synthesis.

The efficacy of ZDV treatment in HIV infection can be attributed to its selective affinity for HIV reverse transcriptase as against human DNA polymerase [7,21]; however, nonspecific inhibition of mitochondrial DNA polymerase- γ results in observed mitochondrial toxicity. Specifically, interference of mitochondrial DNA replication by ZDV-TP results in the reduction of mitochondrial DNA, subsequently leading to mitochondrial dysfunction, with anaerobic respiration, lipoatrophy, myopathy, and lactic acidosis with hepatosteatosis [22–27]. These undesirable side effects are further potentiated in HIV patients because of the negative impact of HIV infection on mitochondria [28]. Because of these factors, the package insert of ZDV includes warnings for the risk of hematological toxicity, myopathy,

and lactic acidosis, with hepatosteatosis being a rare but life-threatening mitochondrial toxicity [29].

Pharmacogenetics

A pilot study addressing the pharmacogenetic characteristics of ZDV therapy in HIV-infected adults reported a trend for elevated ZDV-TPs in *ABCC4* G3724A (rs11568695) variant carriers. The median ZDV-triphosphate concentration was 49% higher in individuals carrying at least one variant allele (AG+AA) than those having the wild type (GG). *ABCB1* (rs2032582) genotype- dependent changes in HIV RNA from baseline to week 52 were observed. Patients with GT or TT experienced significantly greater reductions in HIV RNA compared with patients with GG [16]. Another study showed a faster oral clearance for ZDV for some *UGT2B7* polymorphisms [30]. *UGT2B7*1c* (rs28365062) carriers had 196% higher ZDV oral clearance than noncarriers. Although very few studies have evaluated pharmacogenomics with respect to ZDV and antivirals overall, the results discussed above indicate that the genetic variation in the genes coding ZDV metabolism may influence the efficacy and toxicity of ZDV therapy. Future studies in large patient cohorts are required to further examine and validate the role of pharmacogenomic factors in ZDV pharmacokinetic/pharmacodynamic. Studies focusing on the evaluation and identification of genomic factors influencing ZDV pharmacodynamics, especially as it relates to mitochondrial toxicity, are lacking in the literature.

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Fig. 1. Schematic representation depicting the metabolism of zidovudine and its mechanism of antiviral action. A fully interactive version is available online at <http://www.pharmgkb.org/pathway/PA165859361>.