

Zidovudine

Brand Name: Retrovir

Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Zidovudine, a synthetic antiretroviral agent, is a nucleoside reverse transcriptase inhibitor (NRTI), and an analogue of the naturally occurring nucleoside thymidine. [1] [2]

HIV/AIDS-Related Uses

Zidovudine was approved by the FDA on March 19, 1987, for the treatment of HIV infection in combination with other antiretroviral agents. Studies indicate that zidovudine in combination with other antiretroviral agents is superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4 counts, and decreasing plasma HIV RNA.[3] [4]

Because monotherapy with any single antiretroviral agent is no longer considered an acceptable option in the treatment of HIV infection, except in the prevention of perinatal transmission of HIV from an HIV infected mother to her child, zidovudine is used in conjunction with other antiretroviral agents for initial antiretroviral therapy in the management of HIV infection in treatment-naïve patients. When zidovudine is included in an antiretroviral regimen that includes other nucleoside reverse transcriptase inhibitors (NRTIs), didanosine or lamivudine is usually preferred, and zalcitabine is considered an alternative. Although two-drug regimens that include only NRTIs are no longer preferred regimens for previously treated adults, several studies have evaluated the efficacy of other two-drug and three-drug regimens containing zidovudine in treatment-experienced patients. Results indicate that regimens that include zidovudine and lamivudine or an HIV protease inhibitor (PI) (e.g., indinavir, ritonavir, saquinavir) are generally more effective than zidovudine monotherapy at increasing CD4 counts and decreasing plasma HIV-1 RNA levels in treatment-experienced patients. Zidovudine has also been used in conjunction with nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), as part of treatment for previously-treated, HIV infected adults.[5]

Zidovudine is also approved for the prevention of vertical transmission of the HIV virus from an HIV infected mother to her fetus, as part of a regimen that includes oral zidovudine administered to the mother beginning at 14 to 34 weeks of gestation, intravenous zidovudine syrup administered to the mother during labor, and zidovudine administered to the neonate for the first 6 weeks of life. However, transmission to infants may still occur in some cases, despite the use of this regimen.[6]

Zidovudine is used in conjunction with lamivudine for postexposure prophylaxis of HIV infection in health care workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with blood, tissues, or other body fluids associated with a risk for HIV transmission.[7]

Pharmacology

Zidovudine is virustatic, acting as a reverse transcriptase inhibitor. Zidovudine is phosphorylated intracellularly to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP), by cellular kinases. Neither zidovudine itself nor its intermediate monophosphate metabolite has in vitro activity against HIV. Further study is needed to determine if the intermediate diphosphate metabolite has antiretroviral activity. Because phosphorylation of zidovudine depends on cellular enzymes rather than viral enzymes, conversion to the active triphosphate derivative occurs in HIV infected and uninfected cells. Following conversion, the pharmacologically-active metabolite inhibits in vitro replication of HIV by interfering with the viral RNA-directed DNA polymerase, reverse transcriptase (RT). ZDV-TP appears to compete with thymidine triphosphate for incorporation into viral DNA by the RT enzyme. After incorporation of ZDV-TP, DNA synthesis is prematurely terminated because the 3'-azido group in the zidovudine molecule prevents further 5' to 3' phosphodiester linkages.[8] Intracellular (host cell) conversion of zidovudine to the triphosphate derivative is necessary for the antiviral activity of the drug; however, activation for antibacterial action does not depend on phosphorylation within

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host cells but rather depends on conversion within bacterial cells.[9]

Zidovudine is absorbed rapidly and almost completely from the gastrointestinal tract, with peak serum concentrations (C_{max}) occurring in adults within 0.4 to 1.5 hours after an oral dose. Zidovudine appears to undergo first-pass metabolism. In fasting adults, about 64% of an oral dose reaches systemic circulation as unchanged drug. C_{max} achieved following administration of zidovudine tablets is equivalent to that following administration of capsules or oral solution; however, absorption following oral administration shows considerable individual variability.[10]

There is limited information on the distribution of zidovudine in the body, but the drug appears to be widely distributed. The apparent volume of distribution for the drug in adults and children with HIV infection is 1.4 to 1.6 l/kg.[11] Zidovudine is distributed into the cerebrospinal fluid (CSF) following both oral and IV administration; distribution to CSF averages 68% of the plasma concentration in children and 60% of the plasma concentration in adults. Time to peak concentration (T_{max}) in serum is 0.5 to 1.5 hours.[12]

Zidovudine is in FDA Pregnancy Category C. There are no adequate and well-controlled studies conducted in pregnant women. In rats, 3,000 mg/kg/day (resulting in C_{max} 350 times the human C_{max}) caused marked maternal toxicity and an increase in the incidence of fetal malformations. Teratogenic effects were not seen in this experiment at doses of 600 mg/kg per day or less. Zidovudine crosses the placenta and is distributed into cord blood, fetal blood, and amniotic fluid as well as fetal liver, muscle, and central nervous system tissue.

Zidovudine is distributed into human milk. Potential toxicities of antiretroviral agents in infants exposed to the drugs via breast milk are unknown. In addition, efficacy of antiretroviral therapy for prevention of postpartum transmission of HIV through breast milk is unknown. Because of the risk of transmission of HIV to an uninfected infant through breast milk, the U.S. Centers for Disease

Control and Prevention (CDC) currently recommends that HIV infected women not breastfeed infants. To monitor maternal-fetal outcomes of pregnant women exposed to zidovudine (or other antiretrovirals), an Antiretroviral Pregnancy Registry has been established. Physicians may register patients online at <http://www.APRegistry.com> or by calling 1-800-258-4263.[13]

Plasma protein binding of zidovudine is low (30% to 38%).[14] Zidovudine is rapidly metabolized via glucuronidation in the liver principally to 3'-azido-3'-deoxy-5'-O-beta-D-glucopyranuronosylthymidine (GZDV).[15]

Following hepatic metabolism, elimination of zidovudine is primarily renal. In adults, 63% to 95% of the dose is excreted in urine, approximately 14% to 18% by glomerular filtration and active tubular secretion. Approximately 72% to 74% of the GZDV metabolite is recovered in urine within 6 hours of administration.[16] The plasma half-life of zidovudine in adults averages approximately 0.5 to 3 hours following oral or IV administration. Following IV administration, plasma concentrations decline in a biphasic manner; half-life in adults is less than 10 minutes in the initial phase and 1 hour in the terminal phase.[17] Current data on the efficacy of removing zidovudine by dialysis vary, but hemodialysis and peritoneal dialysis appear to have a negligible effect. Hemodialysis does enhance the elimination of GZDV; however, dialysis clearance of GZDV is minimal compared to the clearance of GZDV in patients with normal renal function.[18]

Emergence of zidovudine resistance appears to be a function of the duration of zidovudine therapy, the severity of HIV disease, and the overall potency of the regimen in which the drug is used. Resistance is most likely to develop in patients with advanced HIV infection, those with low initial absolute helper/inducer T-cell counts, and those receiving prolonged zidovudine therapy. Although it has been suggested that zidovudine resistance may develop at a slower rate in patients with asymptomatic HIV infection than in those with more advanced disease, high-level zidovudine resistance has emerged in patients with asymptomatic infection, especially in those who have received up to 3 years of

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zidovudine monotherapy.[19]

Although the mechanisms of resistance or reduced susceptibility to NRTIs have not been fully determined to date, specific mutations of HIV RT at critical codons on the pol gene fragment have been associated with zidovudine resistance. Zidovudine resistance develops in a progressive, stepwise manner, and each reduction in susceptibility appears to be associated with the acquisition of an additional mutation in the HIV RT gene. The degree of resistance appears to depend on the number and combinations of these mutations.[20]

Further study is needed to more fully evaluate the extent of cross resistance among the NRTIs. Some in vitro studies indicate that zidovudine-resistant HIV generally is susceptible to didanosine, zalcitabine, and stavudine; however, some zidovudine-resistant strains may also be cross resistant or have decreased susceptibility to other NRTIs, including didanosine, lamivudine, stavudine, and zalcitabine. The mutation at position 151 appears to play an important role in the development of multidrug resistance. The pattern of mutations with combination therapy is different from that seen with zidovudine monotherapy. Cross resistance between zidovudine and PIs is unlikely, because these drugs have different target enzymes. The potential for cross resistance between zidovudine and NNRTIs is also considered low, because the drugs bind at different sites on the RT enzyme and have different mechanisms of action.[21]

Adverse Events/Toxicity

Zidovudine has been associated with hematologic toxicity, including neutropenia, leukopenia, and severe anemia, particularly in patients with advanced HIV disease. Prolonged use of zidovudine has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals.[22]

The most frequent adverse effects of zidovudine are granulocytopenia and anemia. These are inversely related to the CD4 count at the start of therapy and directly related to dosage and duration of therapy. Significant anemia most commonly occurs after 4 to 6 weeks of therapy. Other adverse effects include changes in platelet count, hepatotoxicity, lactic acidosis, myopathy, neurotoxicity, severe headache, insomnia, myalgia, nausea, changes in pigmentation, hyperpigmentation of nails, and bone marrow depression.[23]

Immune reconstitution syndrome has been reported in some patients treated with combination antiretroviral therapy, including zidovudine. During the initial phase of combination antiretroviral therapy, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection[24], cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.[25]

In monotherapy clinical studies using zidovudine, the most common adverse events reported were headache, malaise, anorexia, and nausea.[26]

Drug and Food Interactions

Concurrent use of blood dyscrasia-causing medications, other bone marrow depressants, and radiation therapy with zidovudine may cause an additive or synergistic myelosuppression requiring dosage reduction of either or both drugs. Concurrent use of clarithromycin and zidovudine results in lower C_{max} and delayed time to peak serum concentration of zidovudine.

Concurrent administration of ganciclovir or interferon alfa with zidovudine is not recommended

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Drug and Food Interactions (cont.)

because severe hematologic toxicity may occur. Patients receiving these medications concurrently should be monitored frequently for abnormalities in hemoglobin, hematocrit, and white blood cell count; dose reduction or discontinuation of one or both of the medications may be necessary.[27]

Concurrent use of probenecid with zidovudine increases serum concentrations and prolongs elimination half-life for zidovudine, resulting in an increased risk of toxicity. In one small trial, a very high incidence of rash was observed in patients receiving probenecid concurrently with zidovudine. Influenza-like symptoms such as myalgia, malaise, and fever have also occurred.[28]

Concurrent use of doxorubicin or ribavirin and zidovudine is not recommended; in vitro studies indicate an antagonistic relationship between doxorubicin or ribavirin with zidovudine.[29] Ribavirin inhibits the phosphorylation of zidovudine to its active triphosphate form, thus antagonizing the in vitro antiviral activity of zidovudine against HIV. These drugs should not be used concurrently.[30]

Low phenytoin plasma levels have been reported in some patients receiving zidovudine. A pharmacokinetic interaction study showed no effect on phenytoin kinetics, but a 30% decrease of zidovudine clearance was observed with concurrent use of phenytoin and zidovudine.[31]

Total serum concentrations of zidovudine increase when atovaquone, fluconazole, methadone, probenecid, or valproic acid are coadministered with zidovudine. Nelfinavir, rifampin, or ritonavir coadministered with zidovudine decreases the total serum concentration of zidovudine.[32]

Concurrent administration of products that also contain zidovudine, including the coformulations of lamivudine and zidovudine and abacavir sulfate, lamivudine, and zidovudine, should be avoided.[33]

Contraindications

Zidovudine is contraindicated in patients who have potentially life-threatening allergic reactions to any

of the components of the formulations. Zidovudine should not be administered concomitantly with any combination product tablets that contain zidovudine as one of the components.[34]

Clinical Trials

For information on clinical trials that involve Zidovudine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Zidovudine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (capsules, solution, and tablets).[35]

Intravenous injection.[36]

Dosage Form: Capsules containing zidovudine 100 mg.[37] [38]

Oral solution containing zidovudine 50 mg per 5 ml in 240 ml bottle.[39] [40]

Film-coated tablets containing zidovudine 300 mg.[41] [42]

Intravenous (IV) infusion containing zidovudine 10 mg/ml in 20 ml single-use vials.[43]

The recommended oral dose of zidovudine in adults who are not pregnant is 600 mg daily (either 300 mg twice daily or 200 mg three times daily).

The recommended dose in pediatric patients ages 6 weeks to 18 years should be determined by body weight or body surface area. Dosing by weight is as follows: For pediatric patients who weigh from 4 kg to less than 9 kg, a total daily dose of 24 mg/kg should be given in equal doses twice or three times daily. For pediatric patients who weigh from 9 kg to less than 30 kg, a total daily dose of 18 mg/kg should be given in equal doses twice or three times daily. For pediatric patients who weigh 30 kg or more 600 mg per day should be given in equal doses twice or three times daily.[44] Dosing by body surface area is available in the prescribing information.

The recommended dosing regimen for

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Dosing Information (cont.)

administration to pregnant women (more than 14 weeks of pregnancy) is 100 mg, five times daily, until the start of labor. During labor and delivery, IV zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous IV infusion of 1 mg/kg/hr (total body weight) until clamping of the umbilical cord. The neonate should receive 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. In patients maintained on hemodialysis or peritoneal dialysis, the recommended dose of zidovudine is 100 mg every 6 to 8 hours.[45]

Storage: Store zidovudine capsules and film-coated tablets between 15 C and 25 C (59 F and 77 F). Capsules may become discolored or brittle as a result of heat and sunlight exposure, so protect capsules from light, heat, and moisture.[46] [47]

Store zidovudine oral solution at 15 C to 25 C (59 F to 77 F).[48] [49]

Store zidovudine for injection concentrate for IV infusion at 15 C to 25 C (59 F to 77 F) and protect from light.[50]

Chemistry

CAS Name: Thymidine, 3'-azido-3'-deoxy-[51]

CAS Number: 30516-87-1[52]

Molecular formula: C₁₀H₁₃N₅O₄[53]

C44.94%, H4.90%, N26.21%, O23.95%[54]

Molecular weight: 267.24[55]

Melting point: 106 C to 112 C[56]

Physical Description: White to beige, odorless, crystalline solid.[57]

Stability: After dilution, zidovudine IV solutions are physically and chemically stable for 24 hours at room temperature, 15 C to 25 C (59 F to 77 F), and for 48 hours if refrigerated at 2 C to 8 C (36 F to 46 F). However, due to the risk of microbial

contamination, diluted solutions should be administered within 8 hours if stored at 25 C (77 F) or within 24 hours if refrigerated at 2 C to 8 C (36 F to 46 F).[58]

Solubility: 20.1 mg/ml in water at 25 C.[59]

Other Names

Azidothymidine[60]

AZT[61]

ZDV[62]

Zidovudina[63]

Further Reading

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Manufacturer Information

Zidovudine
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

Zidovudine
Cipla Ltd
Mumbai Central
Mumbai, India
912223082891

Retrovir
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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