

## Zidovudine

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KEY WORDS

antiretroviral regimens; HIV-1 infection; mother-to-child HIV-1 transmission

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**Z**idovudine (Retrovir™) is one of the best known agents used in the treatment of women with human immunodeficiency virus type-1 (HIV-1) infection. This generally well-tolerated agent has become a mainstay for the prevention of mother-to-child HIV-1 transmission and is often a component of combination antiretroviral regimens utilized for the treatment of both adult and pediatric HIV-1 infected individuals.

### STRUCTURE AND DERIVATION

Zidovudine (ZDV, AZT, 3'-azido-3'-deoxythymidine) is a synthetic nucleoside analogue of a naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido (-N<sub>3</sub>) group (Fig. 1).

### MECHANISM OF ACTION

Zidovudine (ZDV, AZT) is one of a class of human immunodeficiency virus type-1 (HIV-1) antiviral agents known as dideoxynucleoside reverse transcriptase inhibitors (NRTIs). ZDV inhibits HIV-1 reverse transcriptase, the enzyme needed to catalyze the synthesis of proviral double-stranded DNA from the RNA template (Fig. 2), and therefore interferes with a critical step in the HIV viral life cycle. The antiviral activity of ZDV depends on the intracellular conversion of the drug to a triphosphate metabolite and requires intracellular host cell kinases for conversion to this active 5'-triphosphate form. The active 5'-triphosphate has an affinity for HIV reverse transcriptase and competes with endogenous triphosphate nucleotides

for incorporation into the newly synthesized proviral DNA. ZDV triphosphate lacks a free 3'-hydroxyl group. In order for nucleic acid replication to occur, the 3'-hydroxyl of a naturally occurring nucleoside is the acceptor for covalent attachment of subsequent nucleosides 5'-monophosphate. When ZDV triphosphate is incorporated, it acts as a chain terminator preventing further elongation of the viral DNA chain.

In addition to ZDV, the other NRTIs that are approved by the Food and Drug Administration (FDA) are didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and lamivudine (3TC). Although the structure and mechanism of action of all the nucleoside analogues are similar, they differ significantly in their intracellular phosphorylation pathways and kinetics, which contribute to differences in their *in vitro* antiretroviral activity and pattern of toxicities. The NRTIs have a wider spectrum of antiviral activity than the other available HIV-1 antiviral agents. Other classes of antiviral agents that have been approved by the FDA for the treatment of HIV disease are non-nucleoside reverse transcriptase inhibitors (NNRTIs), which include nevirapine and delaviridine, and the HIV protease inhibitors which include zalcitabine, saquinavir, indinavir, and nelfinavir. HIV protease inhibitors have greater activity than either NRTIs or NNRTIs against HIV-1; these compounds were specifically designed based on the structure of the HIV protease enzyme and have a spectrum of activity limited to HIV-1 and to a lesser extent HIV-2.

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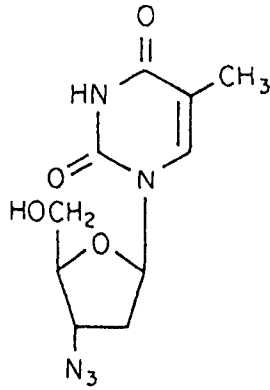


Fig. 1. Structure of zidovudine (ZDV, AZT, 3'-azido-3'-deoxythymidine).

### PHARMACOKINETICS

Zidovudine is rapidly absorbed by the gastrointestinal tract following oral administration with peak serum concentrations occurring within 0.4–1.4 hours. Absorption shows considerable interindividual variation and is influenced by the time and content of the last meal. Once absorbed, prior to systemic distribution, zidovudine undergoes significant first-pass metabolism, giving an average bioavailability of 63%. Zidovudine is approximately 25% protein bound, primarily to albumin. Zidovudine distributes into cells by passive diffusion and is relatively lipophilic; it can be detected in fluids other than plasma, which contributes to its large distribution volume. Zidovudine is primarily metabolized by liver through hepatic 5'-glucuronidation, forming a stable glucuronidated metabolite (GZDV) that is excreted by the kidneys. Approximately 14–20% of unchanged drug and 60–70% of its major metabolite are excreted in the urine following oral or intravenous administration.<sup>1</sup>

Administration of the same standard dose of oral zidovudine results in a variable plasma concentration among adults. The variability is a consequence of between-patient differences in the absorption, distribution, metabolism, and clearance of the drug.<sup>1</sup> Although the plasma pharmacokinetic characteristics have been well studied, the therapeutic range of ZDV and the importance of intracellular pharmacokinetics are not completely understood. Therefore, the optimal dosing strategy for ZDV has not been determined. Recommended doses (see Table 1) are based on clinical endpoints, and not on pharmacodynamic considerations.

Pharmacokinetics in pregnancy have been studied.<sup>2–4</sup> ZDV and GZDV have been detected in the fetus, amniotic fluid, and breast milk. Transplacental transfer of ZDV is by passive diffusion,<sup>5</sup> therefore, maternal plasma concentrations will be a major determinant of fetal concentrations.<sup>6,7</sup> Pregnancy introduces additional sources of variability in the plasma drug concentration, including changes in volume of distribution (expanded plasma volume, increased adipose tissue and the addition of a fetal compartment), changes in drug clearance (increase in cardiac output and a concomitant increase in renal blood flow), and increases in hepatic metabolism. Preliminary reports of zidovudine disposition in obese pregnant women found that achievable plasma concentrations were far lower than expected based on population pharmacokinetic information.<sup>8</sup> In addition, information from the AIDS (acquired immunodeficiency syndrome) Clinical Trial Group (ACTG) 076 study suggests that maternal obesity may be a risk factor for the failure of ZDV prophylaxis to prevent perinatal HIV-1 transmission. (R. Sperling, personal communication)

### CLINICAL APPLICATIONS (DEMONSTRATED EFFICACY) Treatment of Adult Patients

Zidovudine has been extensively studied in the treatment of patients with HIV infection whose CD4+ cell counts are  $\leq 500$  cells/mm<sup>3</sup>. In initial studies, ZDV reduced the risk of disease progression, opportunistic infections, and death in patients with advanced HIV disease.<sup>9</sup> Further experience with the drug revealed that the clinical benefits of ZDV monotherapy were not sustained over the long term. Recent studies have shown that the use of ZDV as part of a combination antiretroviral regimen results in suppression of viral replication and greater clinical benefits, including survival outcome, when compared with ZDV alone.<sup>10</sup>

### Prevention of Mother-to-Child HIV-1 Transmission

In February 1994, the National Institutes of Health (NIH)-sponsored ACTG 076 study was closed to enrollment and unblinded when an interim analysis demonstrated that a regimen that combined maternal and newborn ZDV could dramatically reduce the risk of mother-to-infant HIV-1 transmission.<sup>11</sup>

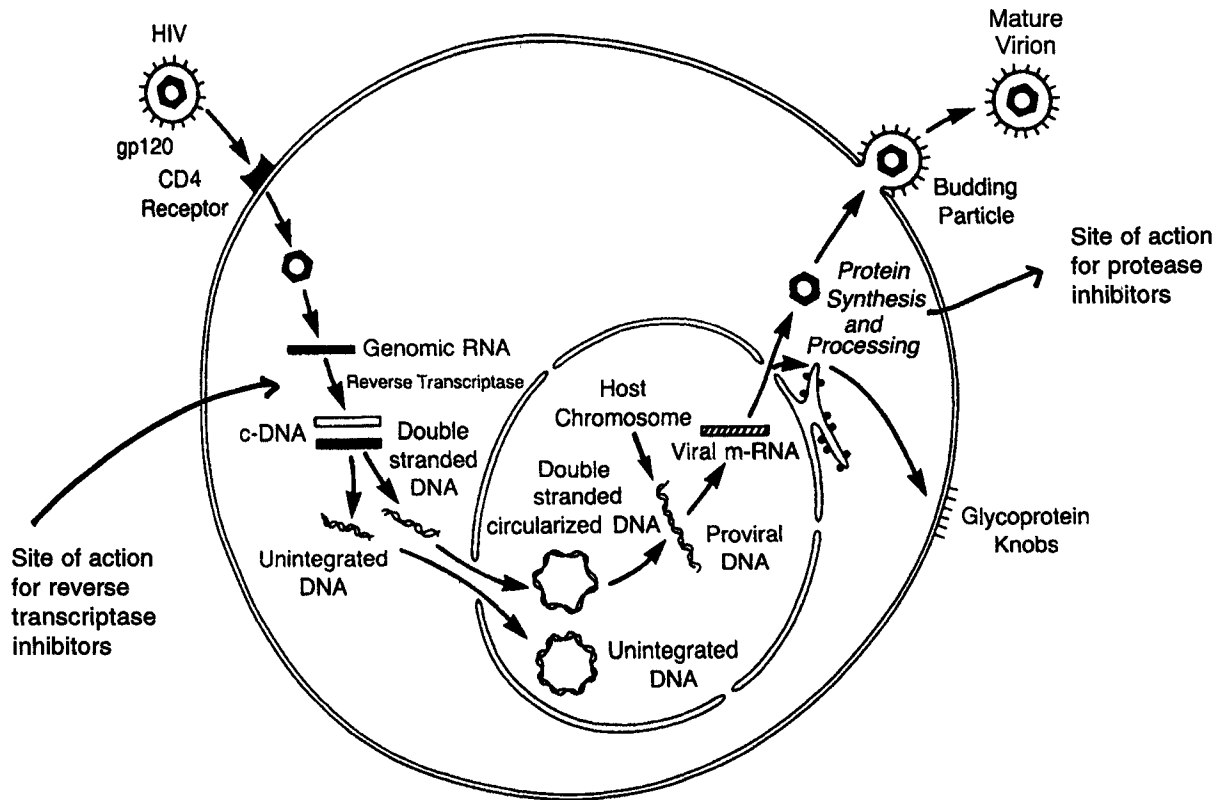


Fig. 2. Life cycle of HIV.

The availability of a regimen that could reduce the transmission of a fatal pediatric disease led the United States Public Health Service<sup>12</sup> to develop consensus guidelines for clinicians about the use of ZDV during pregnancy. Since implementation of these guidelines, additional information about the efficacy of ZDV for the prevention of perinatal transmission has become available.

In November 1996, an efficacy update from the ACTG 076 study confirmed the interim findings. The original report was a Kaplan-Meier estimate of the transmission risk and was based on 363 mother-infant pairs. The recent update included 402 mother-infant pairs, all of whom had completed the 18-month infant follow-up; the rate of HIV-1 transmission was 7.6% with ZDV treatment and 22.6% with placebo ( $P = < .001$ ).<sup>13</sup>

In March 1997, enrollment in another pediatric ACTG study, Protocol 185, was stopped due to an unexpectedly low transmission rate in both study arms.<sup>12</sup> The ACTG 185 was a randomized, controlled clinical trial which compared HIVIG (an immunoglobulin preparation containing high levels of antibodies to HIV) to IVIG (standard immunoglob-

ulin) to determine whether HIVIG could further reduce the risk of mother-to-child transmission if it was added to the maternal-child ZDV regimen successfully utilized in ACTG 076. The ACTG 185 study was designed for women with more advanced immunosuppression than the 076 study. In ACTG 076, all women had CD4+ T-cell counts exceeding 200 cells/mm<sup>3</sup>, and only 5% had received any prior ZDV; in contrast, in ACTG 185, 23% had baseline CD4+ cell counts less than 200 cells/mm<sup>3</sup>, and 21% of women had received prior ZDV. After analyzing outcomes in 379 infants, the estimated overall rate of mother-to-infant HIV transmission was 4.8% with no difference between HIVIG and IVIG recipients.<sup>14</sup> The utility of prophylactic ZDV in pregnant women with advanced immunosuppression that was demonstrated in ACTG 185 is consistent with other reports.<sup>15,16</sup>

In February 1998, enrollment in a trial conducted by the Ministry of Public Health of Thailand (in collaboration with the Centers for Disease Control and Prevention [CDC]) was stopped when an interim analysis demonstrated the success of a short-course of maternal antepartum/intrapartum

TABLE 1. Zidovudine dosing considerations

Medication	Mode of action	Dosage form	Dosing	Major toxicities	Drug interactions	Pregnancy considerations
Zidovudine (AZT, ZDV, Retrovir)	Nucleoside reverse transcriptase inhibitor (NRTI)	100 mg capsules 300 mg tablets Syrup: 50 mg/ml IV: 10 mg/ml	<b>Adults:</b> 100 mg orally 5 times per day (dose studied in perinatal prevention trials) 200 mg orally 3 times per day 300 mg orally twice a day	<b>Most frequent:</b> Bone marrow suppression (anemia and granulocytopenia)  Nausea, myalgias, headaches, and insomnia are common and diminish over time	Co-administration with ganciclovir, alpha-interferon, dapsone, flucytosine, or vincristine can increase hematologic toxicity  Phenytoin and fluconazole can effect ZDV levels	<b>Category: C</b>  <i>Transplacental passage: yes</i>  <i>Animal safety: high doses during late gestation associated with transplacental carcinogenicity in mice</i>  <i>Human safety: extensive experience; reversible anemia in the newborn; long-term safety is being studied</i>
		Also available in combination with 3TC (Combvir-AZT 300 mg/3TC 150 mg)	<b>Intravenous in labor:</b> 2 mg/kg loading dose, followed by continuous infusion of 1 mg/kg/hr  <b>Intravenous newborn intermittent infusion:</b> 1.5 mg/kg every 6 hours  <b>Pediatrics:</b> 90–180 mg/m <sup>2</sup> orally every 6–12 hr  <i>Special considerations:</i> Dose interruption for severe anemia or granulocytopenia	<b>Less frequent:</b> Long-term administration has been associated with peripheral myopathy  Marked elevations in liver function tests, hepatomegaly, and lactic acidosis secondary to steatosis has been reported	Follow-up of children exposed in utero is recommended	

zidovudine therapy for the prevention of mother-to-child HIV-1 transmission.<sup>17</sup> When ZDV, 300 mg twice daily, was given from 36 weeks of gestation until the onset of labor and then increased to 300 mg orally every three hours in labor, the transmission rate was decreased by 51%; the Kaplan-Meier estimates of transmission risk were 9.2% in the placebo group and 18.6% in the placebo group, *P* = 0.008. These findings are consistent with observational studies in the United States<sup>15,16</sup> and provide substantial scientific support for using shorter courses of zidovudine when the complete 076 regimen cannot be given.

Results of all three clinical trials are consistent with the mounting epidemiologic evidence supporting the use of ZDV regimens to prevent mother-to-child HIV-1 transmission:

TABLE 2. Zidovudine regimen studied in ACTG 076

Antepartum dose	Intrapartum dose	Newborn dose
100 mg orally 5 times a day, initiated between 14 and 34 weeks of gestation and continued until labor	2 mg/kg loading dose, followed by continuous infusion of 1 mg/kg/hr	2 mg/kg orally every 8–12 hours, initiated within 8–12 hours of birth and continued for 6 weeks

- Nationwide, the number of cases of pediatric AIDS reported to the CDC declined 47% between 1992 and 1996.<sup>18</sup>
- In North Carolina, mother-to-child transmission rates have decreased from 21% in 1993 to 6% in 1996 following the use of ZDV.<sup>19</sup>

- In New York City, in a cohort of 898 children followed between July of 1994 and June of 1996, the transmission rate was 13% in those mother-infant pairs who received any ZDV, compared with 26% in mother-infant pairs who received no ZDV.<sup>20</sup>
- In New York State, an observational study of 943 HIV-exposed infants born after August 1995 found a transmission rate of 6.3% among infants exposed to the full 076 regimen, an 11.5% transmission rate among infants exposed to ZDV starting either in labor or in the immediate neonatal period, and a 26.5% transmission rate among infants who received no ZDV prophylaxis.<sup>21</sup> This is the first report that supports the efficacy of intrapartum/newborn regimens and even newborn regimens alone if initiated within 48 hours of birth.

### ZDV MECHANISM OF ACTION AS CHEMOPROPHYLAXIS

At the time of the interim ACTG 076 study analysis, the mechanism by which ZDV reduced the risk of transmission was unknown.<sup>11</sup> It is now known, through analysis of viral loads in maternal plasma samples from entry and delivery, that ZDV appears to act primarily by a mechanism other than the reduction of maternal viral burden. Neither the change in maternal plasma viral load from entry to delivery nor a critical level at delivery fully accounts for the substantially reduced transmission rate observed in the ZDV treated group. The possibility of a significant prophylactic effect in utero and/or intrapartum (both during and after exposure) has been raised.

#### Side Effects

##### *Drug Toxicities in Adult Trials*

Early studies utilizing 1200 mg/d reported significant patient problems with drug-associated toxicities. Later studies demonstrated the efficacy of 500–600 mg/d with significantly reduced toxicity. The major side effects include anemia and/or granulocytopenia, headache, fatigue, malaise, nausea, and other gastrointestinal discomforts. Long-term ZDV therapy has been associated with myopathy and rare cases of hepatic steatosis and lactic acidosis.

##### *Drug Toxicities in Perinatal Transmission Trials*

There remains ongoing concerns about the safety of the 076 regimen, both for the mother and for the infant. Specific questions have been raised regarding adverse effects of this regimen on the long-term health of uninfected infants and on maternal disease progression.

The only infant toxicity associated with the ACTG 076 regimen has been a mild, reversible anemia whose nadir has been at 6 weeks of age with resolution by 12 weeks of age. Infant anemia was not associated with the duration of maternal zidovudine treatment. Among uninfected infants in the ACTG 076 study, there were no differences between the zidovudine-exposed infants and the placebo infants in growth patterns, immunologic parameters (lymphocyte subsets), or the occurrence of childhood neoplasias.<sup>22</sup> The Antiretroviral Pregnancy Registry, a collaborative prospective registry supported by pharmaceutical manufacturers, has not found an association between ZDV exposure and congenital anomalies among the cases that have been reported to date.<sup>23</sup>

There is no standard battery of safety tests in animals that are required before a drug is approved by the FDA for use in humans. Although animal testing is frequently performed to assess pregnancy safety, animal data may be difficult to interpret and may not accurately predict risks to human pregnancy. Safety concerns about the use of ZDV in pregnancy have included concerns about potential transplacental carcinogenicity. Theoretically, nucleoside analogs such as ZDV can interfere with DNA synthesis and are potential carcinogens. In one rodent model, high doses of zidovudine given during pregnancy were not associated with adverse outcomes in offspring, including the development of tumors.<sup>24</sup> In another model, extremely high doses of zidovudine administered during pregnancy were associated with an increased risk of tumors in offspring.<sup>25</sup> An NIH panel comprised of clinicians, scientists, and patient advocates reviewed all available animal data and unanimously concluded that the benefits of zidovudine in reducing perinatal HIV far outweighed the potential risks. Other recommendations of this panel included the need to inform women of these data, to conduct long-term follow-up on all children ex-

posed in-utero to ZDV, and to conduct more clinical and basic research on the topic.

In ACTG 076, at 6 months postpartum, there were no differences in clinical, immunologic, or virologic disease progression between those women who received the 076 ZDV regimen and those who received placebo.<sup>20</sup>

### ZDV Resistance

Monotherapy with antiretroviral agents has been associated with drug resistance. Drug resistance is more likely to emerge with increasing duration of therapy and with advancing immunosuppression. In the ACTG 076 study, maternal therapy was not associated with the development of high level zidovudine resistance.<sup>26</sup>

### Cost

ZDV is available in a variety of different formulations (Table 1). Based on average wholesale prices, the unit cost of the 100-mg capsule is \$1.59, the unit cost of the 300-mg tablet is \$4.78, and the unit cost of a 200-mg bottle for intravenous injection is \$17.30. Cost-effectiveness analyses have estimated that the ZDV drug cost per treated case following the ACTG 076 regimen is \$895.<sup>27</sup>

### SUMMARY

Zidovudine was the first agent approved for treatment of HIV disease, and since its widespread availability in 1987, the pharmacokinetic disposition and clinical effects of ZDV have been extensively evaluated. In addition to its utility as a component of a multidrug combination regimen for the treatment of adult and pediatric HIV-1 infection, it is the only agent approved by the FDA for the prevention of mother-to-child HIV-1 transmission.

The effectiveness of ZDV for the prevention of mother-to-child HIV-1 transmission has been demonstrated in several studies. The optimal time during gestation to initiate ZDV therapy and the relative importance of the intrapartum and newborn components is the focus of both current interventional and observational studies. Until more information is available from these trials, the combined maternal/newborn ZDV regimen studied in ACTG 076 remains the recommended treatment regimen of choice in the United States.

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