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# Pharmacokinetic Individualisation of Zidovudine Therapy

## Current State of Pharmacokinetic- Pharmacodynamic Relationships

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### Summary

Zidovudine is the cornerstone of current antiretroviral treatment of human immunodeficiency virus (HIV) infection. Its use, however, frequently leads to adverse reactions, including myelosuppression. Zidovudine pharmacokinetics show large interindividual variation with indications of pharmacokinetic-pharmacodynamic relationships, but a clear therapeutic window has not yet been defined. Individualisation of zidovudine therapy with monitoring of drug concentrations might be desirable. This review considers (intracellular) monitoring of zidovudine and anabolites for individualisation of zidovudine therapy and the achievements in describing pharmacokinetic-pharmacodynamic relationships so far.

## 1. Overview

Zidovudine (ZDV, AZT, 3'-azido-3'-deoxythymidine, Retrovir<sup>®</sup>; fig. 1), developed in the 1960s as an anticancer agent,<sup>[1]</sup> was proven by Mitsuya et al. in 1985 to be an *in vitro* inhibitor of the replication of human immunodeficiency virus (HIV) type 1.<sup>[2]</sup> Since then, zidovudine has quickly passed phase I, II and III trials and today it plays a pivotal role in the treatment of HIV infection.<sup>[3]</sup> Zidovudine prolongs the life of individuals with the acquired immune deficiency syndrome (AIDS), delays progression to AIDS in asymptomatic HIV type 1-infected individuals, and prevents and improves AIDS dementia.<sup>[3-5]</sup> However, it is no cure for HIV infection. Zidovudine is increasingly administered in combination with other antiretroviral agents.<sup>[3]</sup> Its pharmacokinetics show large interindividual variation and no clear therapeutic window has been defined yet. Zidovudine plasma concentrations are not individually monitored in current practice. However, indications of pharmacokinetic-pharmacodynamic relationships are available in the literature. In this article, we present a concise overview of the postulated mechanisms of the anti-HIV action and toxicity of zidovudine, and we review the indications of pharmacokinetic-pharmacodynamic relationships reported to date. Furthermore, we discuss the possibility of individualising zidovudine therapy, by (intracellular) monitoring of zidovudine and/or its metabolites.

## 2. Mechanisms of Antiviral Action and Toxicity of Zidovudine

Zidovudine is a prodrug and must be activated in the target cell by host cellular enzymes to form the 5'-triphosphate derivative, in order to elicit its antiretroviral activity. This process (anabolic phosphorylation) is catalysed by a series of cellular kinases, which also phosphorylate endogenous thymidine. HIV does not code for its own kinases, nor does it have any mechanism for the stimulation of host cellular kinases.<sup>[6]</sup> After passive diffusion of zidovudine into the cell,<sup>[7]</sup> zidovudine 5'-monophosphate (ZDV-MP) formation from zidovudine

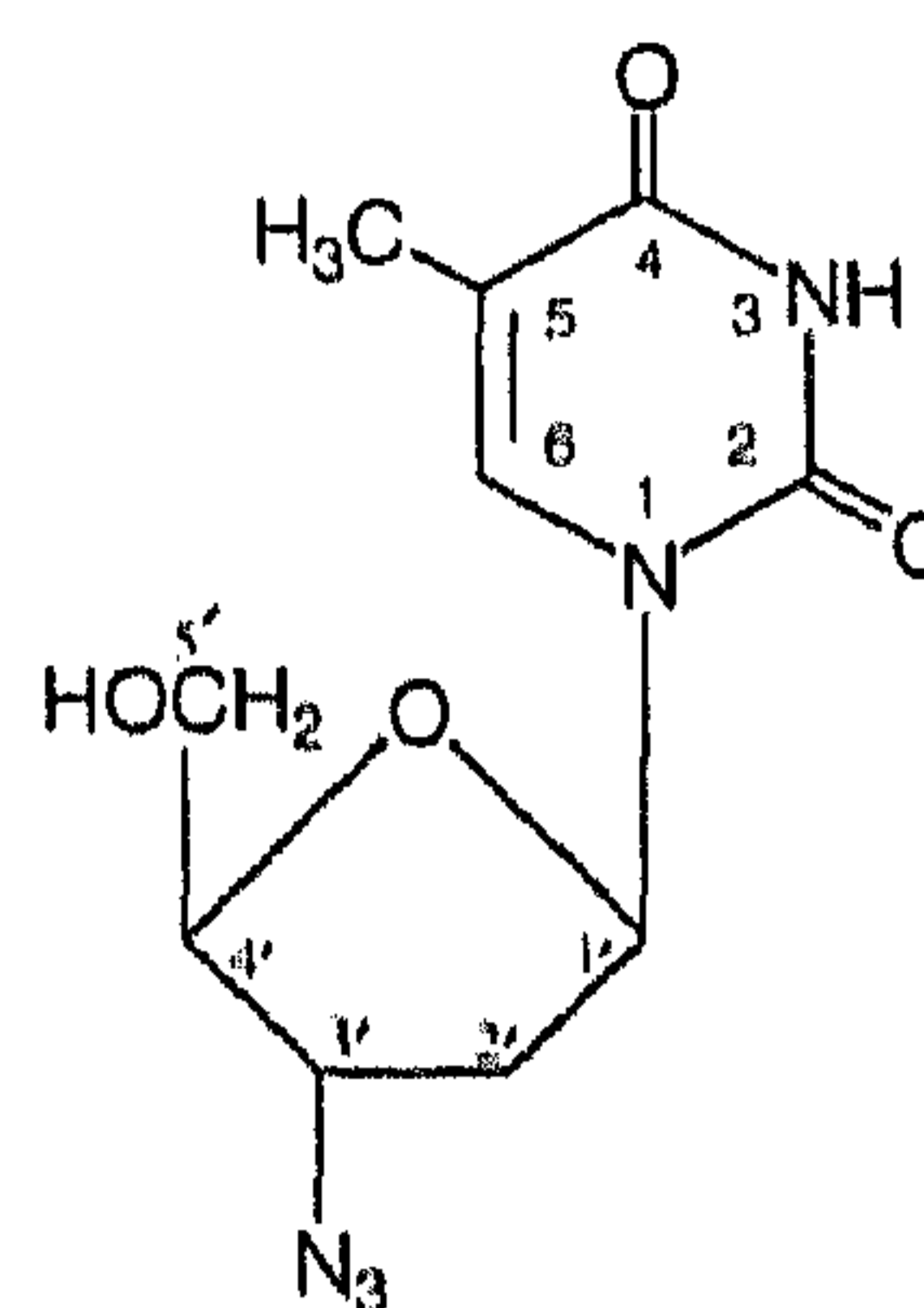


Fig. 1. The chemical structure of zidovudine.

is catalysed by thymidine kinase.<sup>[8]</sup> Thymidylate kinase is the enzyme catalysing the subsequent formation of zidovudine 5'-diphosphate (ZDV-DP)<sup>[8]</sup> and a nucleotide diphosphate kinase catalyses the formation of the active zidovudine 5'-triphosphate (ZDV-TP) from ZDV-DP.<sup>[9-11]</sup>

ZDV-TP inhibits the replication of HIV in 2 main ways. First, it competes with endogenous thymidine 5'-triphosphate for incorporation into proviral DNA, catalysed by the viral reverse transcriptase;<sup>[12,13]</sup> and secondly, incorporation of ZDV-TP in the growing proviral DNA chain leads to chain termination. Because of the missing 3'-hydroxyl group in zidovudine, the usual phosphodiester linkage cannot be built further.<sup>[14-18]</sup> Furthermore, ZDV-MP may decrease HIV replication by inhibiting ribonuclease H (RNase H) activity, an essential part of reverse transcriptase involved in transcriptional processing.<sup>[19]</sup>

Toxicity (mainly myelosuppression) attributed to the use of zidovudine is postulated to be caused by multiple mechanisms. Although ZDV-TP shows higher affinity for the viral polymerase (reverse transcriptase) than for cellular polymerases,<sup>[8,15,20,21]</sup> competitive inhibition of these cellular polymerases may lead to decreased cellular DNA production.<sup>[8]</sup> DNA polymerase  $\alpha$  appears to be relatively resistant to the effects of ZDV-TP, but polymerase  $\gamma$  (in mitochondria) and polymerase  $\beta$  are more sensitive.<sup>[9,22]</sup> Furthermore, incorporation of ZDV-TP in the growing cellular DNA chain causes chain

termination.<sup>[8,23-25]</sup> This may lead to impaired cellular DNA synthesis and subsequent cell dysfunction.

ZDV-TP is not the only anabolite suspected of causing toxicity, ZDV-MP has also been associated with it. This anabolite easily accumulates intracellularly, since the conversion of ZDV-MP to ZDV-DP is the rate-limiting step in the anabolic phosphorylation of zidovudine.<sup>[26]</sup> Accumulation of ZDV-MP may lead to inhibition of the formation of thymidine 5'-triphosphate by inhibition of thymidylate kinase, thus impairing cellular DNA synthesis.<sup>[27]</sup> The inhibition of exonuclease activity by ZDV-MP has been reported.<sup>[22]</sup> An exonuclease excises ZDV-MP from cellular DNA and may thus prevent cytotoxicity caused by zidovudine.<sup>[22,25]</sup>

It is not only intracellular metabolism that may generate cytotoxic metabolites of zidovudine. Reduction of the 3'-azido function of zidovudine in liver microsomes yields the extracellular metabolite 3'-amino-3'-deoxythymidine (AMT, 3A3D), a potentially toxic metabolite after intracellular phosphorylation.<sup>[28]</sup>

Furthermore, zidovudine is reported to affect intracellular (deoxy)nucleoside triphosphate pools, thereby possibly modulating the effects and/or toxicity of zidovudine.<sup>[8,29,30]</sup>

### 3. Plasma Pharmacokinetics of Zidovudine

The pharmacokinetic profile of zidovudine has been extensively reviewed in the literature,<sup>[6,31-34]</sup> updated in a review in this issue of *Clinical Pharmacokinetics*,<sup>[35]</sup> and is briefly discussed in this section. A representative zidovudine plasma concentration-time profile after an oral dose of 200mg is presented in figure 2.<sup>[36]</sup>

#### 3.1 Absorption

Zidovudine is rapidly and completely absorbed after oral administration and has a bioavailability of approximately  $64 \pm 10\%$ .<sup>[37-39]</sup> Mild diarrhoea yields lower<sup>[40]</sup> or similar<sup>[41]</sup> bioavailability, while dose size (250 to 1250mg) has no influence.<sup>[37]</sup> After administration of a 200mg capsule, a peak plasma

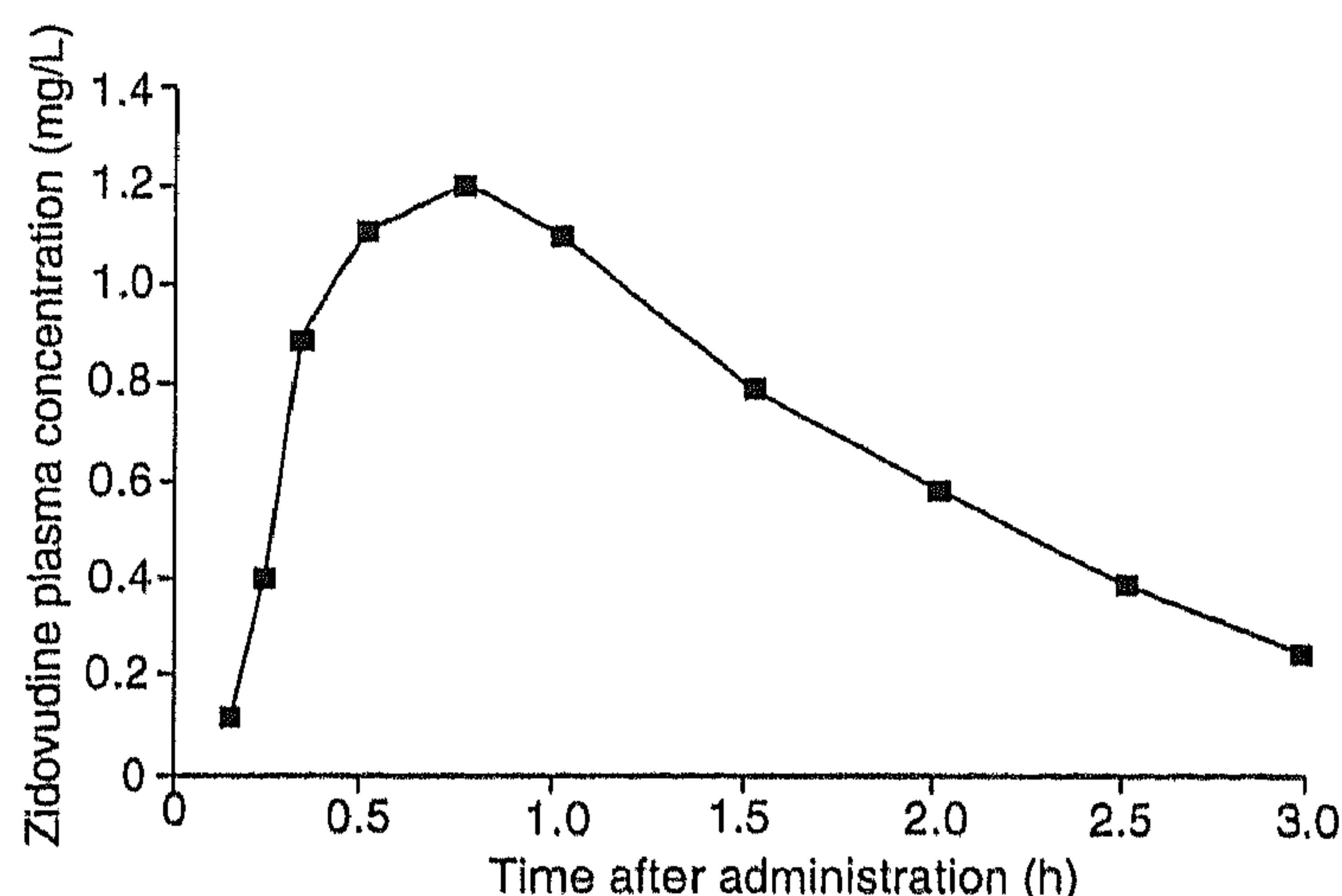


Fig. 2. Representative plasma concentration-time profile of zidovudine (200mg oral dose).

zidovudine concentration ( $C_{max}$ ) of approximately 1.2 mg/L is reached after about 0.75 hours ( $t_{max}$ ).<sup>[42]</sup> In general, concomitant administration of zidovudine with food decreases  $C_{max}$  and  $t_{max}$ , but plasma area under the concentration-time curve (AUC) values are unaffected.<sup>[43-47]</sup>

#### 3.2 Distribution

Zidovudine is widely distributed in body fluids and tissues with a steady-state volume of distribution ranging from 1.4 to 3.9 L/kg.<sup>[37,39,48]</sup> Plasma protein binding ranges from 7 to 38%.<sup>[31]</sup> Distribution of zidovudine into saliva has been reported and a correlation between zidovudine concentrations in citric acid-stimulated saliva and concurrent plasma samples has been observed.<sup>[49]</sup> Data concerning the distribution of zidovudine in body fluids other than blood or saliva have been discussed in several reviews.<sup>[6,31-34,50]</sup>

#### 3.3 Metabolism and Elimination

Zidovudine is eliminated from the body by metabolism in the liver and by renal microsomes,<sup>[51]</sup> renal excretion of the parent compound and metabolites, and uptake by cells and subsequent conversion to ZDV-TP. Its plasma clearance is approximately 1.3 L/h/kg, with an elimination half-life ( $t_{1/2}$ ) of 1 hour.<sup>[37,39]</sup> Zidovudine is extensively metabolised, mainly to an inactive glucuronide (ZDV-G) which is excreted renally. After oral administration

approximately 14% of the dose is excreted unchanged in the urine and approximately 75% is recovered as a glucuronide.<sup>[37]</sup> The plasma concentration of ZDV-G is generally higher than that for zidovudine; thus, the clearance of this metabolite is lower than that of the parent drug. A parallel decay of both plasma concentration profiles is observed,<sup>[33]</sup> suggesting formation-limited elimination of ZDV-G and a smaller volume of distribution of the glucuronide compared with its parent drug. Furthermore, zidovudine is metabolised in the liver to AMT.<sup>[28]</sup> A schematic overview of the metabolic and elimination pathways of zidovudine is depicted in figure 3.

#### 4. Intracellular Pharmacokinetics of Zidovudine and Anabolites

Several investigators have measured intracellular concentrations of the various zidovudine nucleo-

tides<sup>[26,27,52-54]</sup> or total zidovudine nucleotides<sup>[55,56]</sup> in peripheral blood mononuclear cells (PBMCs) or assayed inhibition of reverse transcriptase as a measure to quantify ZDV-TP.<sup>[57]</sup> The pharmacokinetic parameters of intracellular zidovudine metabolism are summarised in tables I and II.

It is clear from table I that ZDV-MP is the most abundant intracellular anabolite of zidovudine. This is consistent with the observation that the formation of ZDV-DP is the rate-limiting step in the activation cascade of zidovudine.<sup>[8-11,26,29]</sup>

As can be seen from table II, the  $t_{1/2}$  of intracellular total phosphorylated zidovudine is approximately 4 hours.<sup>[56,60]</sup> This allows a dose interval of at least 8 hours instead of the initial 4 hours, based on the zidovudine plasma  $t_{1/2}$  of 1 hour.<sup>[56]</sup>

The observed differences in pharmacokinetic parameters in tables I and II could be caused by differences between the analytical techniques used and/or by biological variation in phosphorylation

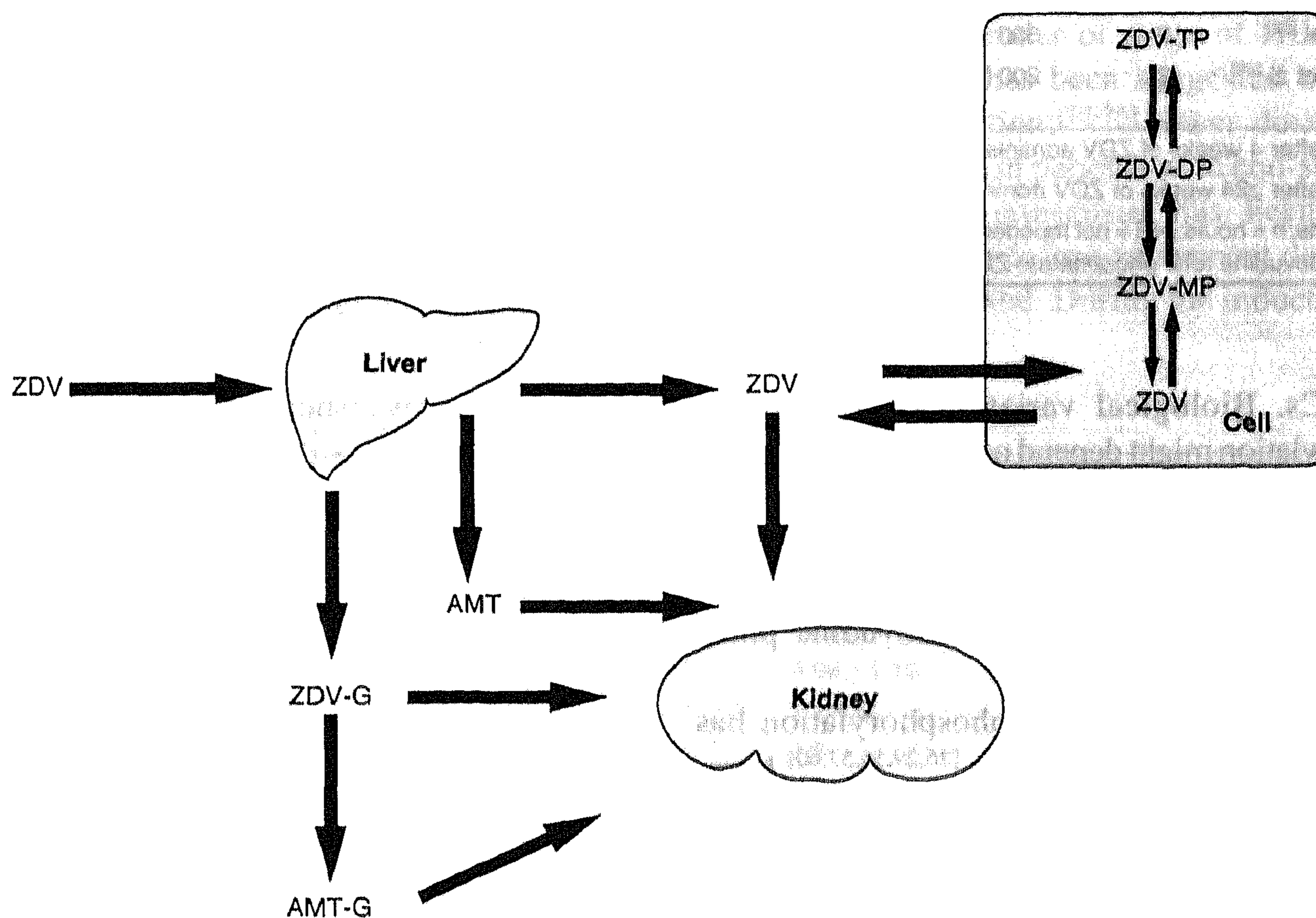


Fig. 3. Schematic representation of the metabolic and elimination pathways of zidovudine. Abbreviations: AMT = 3'-amino-3'-deoxythymidine; AMT-G = 3'-amino-3'-deoxythymidine glucuronide; ZDV = zidovudine; ZDV-G = zidovudine glucuronide; ZDV-MP = zidovudine monophosphate; ZDV-DP = zidovudine diphosphate; ZDV-TP = zidovudine triphosphate.

**Table I.** Intracellular amounts of oral zidovudine (ZDV) and anabolites

Reference	No. of patients	Dose (mg)	Amounts of intracellular ZDV and anabolites (pmol/10 <sup>6</sup> cells) [time (h) after administration]					
			ZDV	ZDVPT (± SD)	ZDV-MP	ZDV-DP	ZDV-TP	
Barry et al. <sup>[27]</sup>	5 <sup>a</sup>	250	NR	NR	0.00-0.31 (1)	NR	0.00-0.15 (1)	
					0.00-0.28 (2)		0.00-0.07 (2)	
					0.00-0.11 (4)		0.00-0.05 (4)	
					0.00-0.10 (6)		0.00-0.16 (6)	
	12 <sup>b</sup>	250	NR	NR	0.12-2.46 (1)	0.00-0.12 (1)	0.00-0.18 (1)	
					0.45-3.96 (2)	0.00-0.21 (2)	0.00-0.22 (2)	
					0.10-1.86 (4)	0.00-0.25 (4)	0.00-0.19 (4)	
					0.13-1.20 (6)	0.00-0.21 (6)	0.00-0.20 (6)	
Kuster et al. <sup>[52]</sup>	3	250	NR	NR	0.7-1.2 (1)	<0.1-0.3 (1)	0.2-0.3 (1)	
					0.6-1.4 (2)	0.2-0.5 (2)	0.2-0.5 (2)	
					0.3-1.1 (4)	<0.1 (4)	<0.1 (4)	
Robbins et al. <sup>[57]</sup>	12	100	NR	NR	NR	NR	0.001-0.049 (1)	
							0.011-0.207 (2)	
							0.011-0.089 (4)	
	12	500	NR	NR	NR	NR	NR	0.024-0.326 (6)
								0.028-0.098 (1)
								0.001-0.182 (2)
Shelton et al. <sup>[58]</sup>	7	100	NR	2.8 ± 3.1	NR	NR	0.019-0.076 (4)	
							0.001-0.207 (6)	
Slusher et al. <sup>[53]</sup>	7	300	0.15 (2)	NR	1.38 (2)	0.082 (2)	0.082 (2)	
Toyoshima et al. <sup>[26]</sup>	2	200	NR	NR	26-50 (1)	0.65 (1)	1.5-5.6 (1)	
					24-26 (4)	0.39 (4)	1.3-1.7 (4)	

a Values after 4 weeks of ZDV administration.

b Values after ≥24 weeks of ZDV administration.

Abbreviations: h = hours; NR = not reported; SD = standard deviation; ZDV-DP = zidovudine diphosphate; ZDV-MP = zidovudine monophosphate; ZDVPT = zidovudine total phosphates; ZDV-TP = zidovudine triphosphate.

in PBMCs. Biological variation of zidovudine phosphorylation might depend on the relative amount of the various mononuclear cells and on their activation state. *In vitro* studies have demonstrated that phytohaemagglutinin-stimulated PBMCs produce approximately 100-times more zidovudine phosphates than resting PBMCs.<sup>[7,60]</sup>

Saturation of zidovudine phosphorylation has been suggested in several studies.<sup>[26,29,56,57,60]</sup> Intracellular concentrations of ZDV-TP level off if extracellular concentrations of zidovudine reach 2 µmol/L (approximately 0.5 mg/L) or higher;<sup>[26]</sup> this may explain the lack of additional benefit of high versus low dosages of zidovudine.<sup>[61-64]</sup> Saturation points probably vary between patients.<sup>[56]</sup>

Recently, it was shown that doxorubicin, ribavirin and AMT decrease the intracellular phosphorylation of zidovudine in PBMCs *in vitro*.<sup>[65]</sup>

Induction of phosphorylating enzymes has not been observed.<sup>[56]</sup> In contrast, several studies have suggested that there may be decreased intracellular phosphorylation of zidovudine with prolonged zidovudine therapy,<sup>[54,56,66]</sup> with the emergence of viral strains less susceptible to zidovudine therapy.<sup>[56]</sup>

In general, the measurement of intracellular anabolites of zidovudine is laborious and cumbersome, and relatively large amounts of blood (10 to 50ml) are required.<sup>[26,27,52-57]</sup>

## 5. Relationship Between Zidovudine Extra- and Intra-Cellular Pharmacokinetics

The efficacy and toxicity of zidovudine are supposed to be largely caused by the effects of its intracellular anabolites (section 2). Several researchers have suggested, therefore, that a relationship could be more easily found between the intracellular pharmacokinetic parameters of zidovudine and its efficacy and/or toxicity.<sup>[27,52,53,55-57,59,67-70]</sup> If no relationship exists between intracellular phosphorylation and plasma pharmacokinetics, the relationship between any plasma pharmacokinetic parameter and efficacy and/or toxicity will thus probably be absent.

In table III, relationships between extracellular and intracellular zidovudine pharmacokinetics, as reported in the literature to date, are summarised. The relevance of the reported relationships between intra- and extra-cellular pharmacokinetic parameters has yet to be proven.

## 6. Inter- and Intra-Individual Variability in Zidovudine Pharmacokinetics

Large inter- and intra-individual differences in the pharmacokinetics of zidovudine have been reported in the literature.<sup>[31,36,71]</sup> Apparent zidovudine clearance is reported to be lower in patients with a

lower bodyweight, in women and in patients with a more advanced stage of HIV disease.<sup>[36]</sup> The apparent volume of distribution of zidovudine probably decreases because of advancing HIV disease.<sup>[48]</sup> Several small studies have revealed that zidovudine  $C_{max}$ , plasma AUC and elimination  $t_{1/2}$  are increased, and  $t_{max}$  and oral clearance decreased, in patients with liver disease. ZDV-G  $C_{max}$  and the ratio of the plasma AUC of ZDV-G : zidovudine is decreased in these patients.<sup>[72-75]</sup> Severe renal impairment causes zidovudine  $C_{max}$ , plasma AUC and  $t_{1/2}$  values to increase, together with a decrease in oral clearance of the drug. Plasma ZDV-G concentrations are markedly increased.<sup>[76,77]</sup> Haemodialysis has a negligible effect on the plasma pharmacokinetics of zidovudine, whereas ZDV-G elimination is enhanced. Furthermore, coadministration of drugs can alter the pharmacokinetic profile of zidovudine.<sup>[78]</sup>

As discussed in section 3.1, the concomitant intake of zidovudine with food can alter the absorption rate of the agent.

Zidovudine dosages are currently not adjusted for bodyweight, gender or stage of HIV disease. Dosage reduction has been suggested in patients with liver dysfunction;<sup>[73-75]</sup> lower dosages have also been proposed in patients with end-stage renal disease.<sup>[77]</sup> Little consensus has been reached whether zidovudine dosage adjustment due to comedication is warranted. During the induction phase

**Table II.** Intracellular pharmacokinetics of oral zidovudine (ZDV) and anabolites

Reference	No. of patients	Dose (mg)	AUC <sup>a</sup> ( $\pm$ SD) (pmol/10 <sup>6</sup> cells $\cdot$ h)	$t_{1/2}$ <sup>a</sup> ( $\pm$ SD) (h)	$C_{max}$ <sup>a</sup> ( $\pm$ SD) (pmol/10 <sup>6</sup> cells)	$t_{max}$ (h)
Barry et al. <sup>[27]</sup>	5	250	0.66 $\pm$ 0.48 <sup>b</sup>	NR	NR	NR
	12	250	5.91 $\pm$ 3.42 <sup>b</sup>	NR	NR	NR
Stretcher et al. <sup>[56]</sup>	20 <sup>c</sup>	100	3.29 $\pm$ 0.97	4.07 $\pm$ 1.13	0.48 $\pm$ 0.18	2.63 $\pm$ 1.36
	18 <sup>d</sup>	100	2.16 $\pm$ 1.09	3.96 $\pm$ 1.10	0.29 $\pm$ 0.18	2.94 $\pm$ 1.59
Stretcher et al. <sup>[59]</sup>	4	100	0.71-4.12	2.1-4.0	0.36-1.73	1.0-2.3
	1	200	8.54	3.5	2.77	1.0
	1	300	6.69	4.2	2.32	1.0

a ZDV total phosphates.

b Determined from zero to 6 hours.

c HIV-seronegative volunteers.

d Patients with AIDS.

Abbreviations: AUC = area under the concentration-time curve;  $C_{max}$  = peak plasma concentration; h = hours; NR = not reported; SD = standard deviation;  $t_{max}$  = time to  $C_{max}$ ;  $t_{1/2}$  = elimination half-life.

**Table III.** Relationship between the extracellular and intracellular pharmacokinetics of oral zidovudine (ZDV)

Reference	No. of patients	Dosage (mg)	Extracellular parameter (ZDV)	Intracellular parameter	Related
Peter & Gambertoglio <sup>[66]</sup>	3	1 × 200	Plasma $t_{max}$	$t_{max}$ of intracellular ZDV, ZDV-MP, ZDV-DP and ZDV-TP	Positively
Robbins et al. <sup>[57]</sup>	12	1 × 100, 1 × 500	Dose, plasma AUC	Amount of ZDV-TP	Positively
Stretcher et al. <sup>[56]</sup>	21	5 × 100	Plasma AUC	ZDVpt AUC	No
			Dose	ZDVpt concentration	Positively
Stretcher et al. <sup>[59]</sup>	6	5 × 200, 3 × 300, 5 × 100	Plasma AUC	ZDVpt AUC	Positively
Stretcher et al. <sup>[69]</sup>	13	5 × 100, 6 × 200, 4 × 60	Dose, plasma concentration	ZDVpt concentration	No

*Abbreviations:* AUC = area under the concentration-time curve;  $t_{max}$  = time to peak plasma concentration; ZDV-DP = zidovudine diphosphate; ZDV-MP = zidovudine monophosphate; ZDVpt = zidovudine total phosphates; ZDV-TP = zidovudine triphosphate.

of ganciclovir therapy, zidovudine administration is often stopped.<sup>[78]</sup>

Once clear pharmacokinetic-pharmacodynamic relationships have been established, the relevance of the reported differences in pharmacokinetic parameters can be better assessed.

Interindividual differences in intracellular zidovudine metabolism have seldom been investigated. In one study it was suggested that women had a significantly higher AUC of total intracellular phosphorylated zidovudine compared with men, though this observation could be caused by insufficient female participants in the study and thus needs to be confirmed.<sup>[55,56]</sup> Furthermore, it has been reported that intracellular amounts of ZDV-TP are similar but amounts of ZDV-MP are higher among more immunosuppressed individuals.<sup>[27]</sup>

## 7. Pharmacokinetic-Pharmacodynamic Relationships

### 7.1 Relationship Between Zidovudine Plasma Pharmacokinetics and Efficacy and/or Toxicity

Monitoring zidovudine plasma pharmacokinetics in order to individualise therapy only makes sense when clear pharmacokinetic-pharmacodynamic relationships exist. In the literature, data regarding these relationships for zidovudine are relatively sparse. Most data can be derived from studies that were not originally conducted and designed to find

pharmacokinetic-pharmacodynamic relationships. In tables IV and V, literature data of the relationship between the plasma pharmacokinetic parameters of zidovudine and its efficacy and toxicity, respectively, are summarised. Zidovudine dosage has been included in these tables as a 'pharmacokinetic parameter'; plasma  $C_{max}$ , plasma AUC and mean plasma concentration increase proportionally with increased zidovudine dosages.<sup>[6,81,85,94]</sup>

The results given in tables IV and V indicate that a relationship between zidovudine pharmacokinetic parameters and toxicity, though not yet always quantified properly, does exist. Relationships between zidovudine pharmacokinetic parameters and antiretroviral efficacy are more difficult to find. A daily oral dosage of zidovudine 150mg (50mg every 8 hours) appeared to produce a sub-optimal effect on p24 antigenaemia and CD4+ lymphocyte counts.<sup>[95]</sup> This result indicates that lowering the dosage of zidovudine may lead to decreased antiviral efficacy. The original zidovudine dosages used are relatively high. It might be that higher zidovudine dosages do not add proportionally to efficacy, but produce more toxicity. The data presented in tables IV and V are consistent with this hypothesis, since efficacy does not seem to increase with higher zidovudine dosages, whereas toxicity does increase.

The primary end-point of antiretroviral therapy is the reduction in mortality. Short term efficacy, however, is measured by changes in surrogate para-



meters such as CD4+ lymphocyte counts, p24 antigenaemia and changes in clinical response (body-weight gain and a reduction in the incidence of opportunistic infections). However, the use of antimicrobial drugs can also influence clinical response.<sup>[34]</sup> Measuring the efficacy of zidovudine therapy is therefore difficult. The measurement of viral load as a marker for the efficacy of anti-retroviral therapy is increasingly accepted as the gold standard.<sup>[96-98]</sup>

It can be concluded that clear zidovudine plasma pharmacokinetic-pharmacodynamic rela-

tionships have not yet been defined. However, several studies indicate that a relationship between plasma pharmacokinetics and toxicity does exist.<sup>[61,63,71,79,82,83,88-93]</sup>

## 7.2 Relationship Between Zidovudine Intracellular Pharmacokinetics and Efficacy and/or Toxicity

Stretcher et al.<sup>[55]</sup> found a weak correlation between the AUC of total intracellular phosphorylated zidovudine and surrogate markers in HIV

**Table IV.** Relationship between plasma pharmacokinetics and efficacy of zidovudine (ZDV)

Reference	No. of patients	Dosage (mg)	Pharmacokinetic parameter (ZDV)	Efficacy	Related
Balis et al. <sup>[79]</sup>	21	0.5, 0.9, 1.4 and 1.8 mg/kg/h continuous infusion	Steady-state plasma or CSF concentration	Change in IQ	No
Chiang et al. <sup>[80]</sup>	104	100-800 mg/day PO	Plasma AUC <sup>a</sup>	Increased CD4+ and CD8+ lymphocyte count, bodyweight	Positively
Collier et al. <sup>[81]</sup>	41	6 × 50, 6 × 100, 6 × 250 PO	Plasma C <sub>max</sub> , AUC	Change in CD4+ lymphocyte count, HIV p24 antigenaemia	No
Collier et al. <sup>[83]</sup>	67	6 × 50, 6 × 100, 6 × 250 PO	Dosage	Change in CD4+ lymphocyte count, HIV p24 antigenaemia, plasma HIV titre, Karnofsky score, fatigue	No
Drusano et al. <sup>[82]</sup>	14	NR, continuous infusion	Steady-state plasma concentration	Change in CD4+ lymphocyte count	No
Fischl et al. <sup>[81]</sup>	524	6 × 250 PO; 6 × 200 (4wk), then 6 × 100 PO	Dosage Dosage	Increased survival up to 24 months after starting therapy Risk of AIDS-defining opportunistic infection, change in CD4+ lymphocyte count, HIV p24 antigenaemia	Negatively No
Gøtzsche et al. <sup>[83]</sup>	474	400, 800 or 1200 mg/day in 4 doses	Dosage	Change in CD4+ lymphocyte count, Karnofsky score, well-being, time to new AIDS-defining event or death	No
Mentré et al. <sup>[71]</sup>	36	4 × 500 (28 days), then 4 × 250 PO	Mean daily concentration, various pharmacokinetic parameters	Occurrence of opportunistic infections	No
Sale et al. <sup>[84]</sup>	217	5 × 100, 5 × 300 PO	Plasma AUC	Change in CD4+ lymphocyte count	No
Stretcher et al. <sup>[55]</sup>	21	5 × 100 PO	Plasma AUC	Change in CD4+ lymphocyte count, ratio CD4+ : CD8+ lymphocyte count, β <sub>2</sub> -microglobulin, neopterin	No
Tartaglione et al. <sup>[85]</sup>	29	6 × 250 PO; 6 × 200 PO (1mo), then 6 × 100 PO	CSF and serum concentration, cumulative dose	HIV isolation from CSF, change in neurological symptoms	No
Volberding et al. <sup>[86]</sup>	1338	5 × 100, 5 × 300 PO	Dosage	Change in CD4+ lymphocyte count, HIV p24 antigenaemia, development of AIDS or advanced AIDS-related complex	No

a Determined from zero to 24 hours.

**Abbreviations:** AUC = area under the concentration-time curve; C<sub>max</sub> = peak concentration; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; IQ = intelligence quotient; mo = month(s); NR = not reported; PO = oral administration; wk = week(s).

**Table V.** Relationship between plasma pharmacokinetics and toxicity of zidovudine (ZDV)

Reference	No. of patients	Dosage (mg)	Pharmacokinetic parameter (ZDV)	Parameter of toxicity	Related
Balis et al. <sup>[79]</sup>	21	0.5, 0.9, 1.4 and 1.8 mg/kg/h continuous infusion	Steady-state plasma concentration	Neutropenia	Positively
Barry et al. <sup>[87]</sup>	12	250-850 PO	Plasma $t_{max}$ , $t_{1/2}$ , AUC normalised to 250mg dose, urinary ratio ZDV-G : ZDV	Bone marrow erythroid aplasia/hypoplasia	No
Baxter et al. <sup>[88]</sup>	10	200	Mean plasma AUC, AUMC, MRT, mean trough concentration	Anaemia	Positively
Collier et al. <sup>[63]</sup>	67	6 × 50, 6 × 100, 6 × 250 PO	Dosage	Granulocytopenia, anaemia	Positively
Drusano et al. <sup>[82]</sup>	14	NR, continuous infusion	Steady-state plasma concentration	Granulocytopenia	Positively
Fischl et al. <sup>[61]</sup>	524	6 × 250 PO; 6 × 200 (4wk), then 6 × 100 PO	Dosage	Neutropenia, anaemia	Positively
Gelmon et al. <sup>[89]</sup>	74	600 mg/day (18wk), then 900 mg/day (9wk), then 1200 mg/day (9wk)	Dosage	Granulocytopenia, anaemia	No
			Dosage	Decreased reticulocyte count	Positively
Gøtzsche et al. <sup>[83]</sup>	474	400, 800 or 1200 mg/day in 4 doses	Dosage	Anaemia, leucopenia, time to first dose reduction, no. of patients withdrawn	Positively
Grau et al. <sup>[90]</sup>	50	NR	Total lifetime cumulative ZDV intake	Percentage of red ragged fibres in muscle biopsy specimens	Positively
Koch et al. <sup>[91]</sup>	1567	5 × 100, 5 × 300 PO	Dosage	Neutropenia, anaemia	Positively
Mentré et al. <sup>[71]</sup>	36	4 × 500 (28 days), then 4 × 250 PO	Mean daily ZDV concentration	Anaemia	Positively
			Dosage	Anaemia	No
Scherpbier et al. <sup>[92]</sup>	12	600 or 800 mg/m <sup>2</sup> /day in 4 doses	Dosage	Granulocytopenia, anaemia	Positively
Stretcher et al. <sup>[55]</sup>	21	5 × 100	Plasma AUC	Neutropenia, anaemia	No
Vocks-Hauck et al. <sup>[93]</sup>	19	4 × 100 mg/m <sup>2</sup> or 4 × 180 mg/m <sup>2</sup>	Plasma AUC	Neutropenia, decreased lymphocyte count	Positively
			Plasma $C_{max}$	Anaemia	Positively

*Abbreviations:* AUC = area under the concentration-time curve; AUMC = area under the first moment-time curve;  $C_{max}$  = peak plasma concentration; MRT = mean residence time; NR = not reported; PO = oral administration;  $t_{max}$  = time to  $C_{max}$ ;  $t_{1/2}$  = elimination half-life; wk(s) = week(s); ZDV-G = zidovudine glucuronide.

disease (percentage of CD4+ lymphocytes and CD4+/CD8+ lymphocyte count ratio) and zidovudine toxicity (haemoglobin) in asymptomatic HIV-infected adults. The correlation was not found for any zidovudine plasma pharmacokinetic parameter.

Others suggest that the ratio of ZDV-TP to thymidine 5'-triphosphate concentration is the major determinant of efficacy, rather than the absolute ZDV-TP concentration.<sup>[27]</sup>

Problems encountered when interpreting the results of intracellular zidovudine phosphate assays (separate or total) are possibly due to different degrees of phosphorylation in the various mononuclear cells (monocytes, T and B lymphocytes) and the intra- and inter-individual variation in mononuclear cell-type distribution.

The following section briefly describes some pharmacokinetic-pharmacodynamic relationships that theoretically might be found in the near future.

## 8. Theoretical Correlations Between Zidovudine Pharmacokinetic and Pharmacodynamic Parameters

When looking at the mechanism of the antiviral activity of zidovudine with a central role played by ZDV-TP, it might be expected that the efficacy of the drug could be correlated best with the intracellular amount of its active metabolite.<sup>[68]</sup> However, the reported inhibitory effect of ZDV-MP on RNase H activity<sup>[19]</sup> might disturb and negatively influence this correlation. Since the main anabolite of zidovudine is ZDV-MP,<sup>[29,60]</sup> correlation between zidovudine efficacy and the intracellular amount of ZDV-MP might also be identified, depending on the relative contribution of the effect of ZDV-MP to the overall antiretroviral effect of zidovudine. Assaying the total amount of intracellular zidovudine anabolites could also be related to zidovudine efficacy, depending on the ratio of zidovudine anabolites and the relative contribution of ZDV-MP and ZDV-TP to the overall antiviral effect. This relationship is less likely to be found if the intracellular metabolism of zidovudine shows large interindividual variation. A relationship between zidovudine toxicity and ZDV-TP concentration might not easily be found, if we consider the saturation of phosphorylation to ZDV-TP at normally achieved zidovudine concentrations.<sup>[26,29,56,57,60]</sup> Zidovudine toxicity might be related to intracellular amounts of ZDV-MP, since ZDV-MP is reported to inhibit exonuclease activity.<sup>[22]</sup> Correlation between zidovudine toxicity and total intracellular zidovudine anabolites might also be found, because ZDV-MP is the most abundant nucleotide formed in the zidovudine anabolism pathway.<sup>[29,60]</sup> Finally, correlations between zidovudine toxicity and AMT plasma or intracellular pharmacokinetic parameters need further exploration to find the relative contribution of this metabolite to overall toxicity.

Presumably, not all mechanisms of the antiretroviral effect or toxicity of zidovudine have been discovered yet and other (combinations of) intra- and/or extracellular parameters of zidovudine pharmacokinetics could correlate better with its

efficacy and/or toxicity. An important feature of such a parameter for use in therapeutic drug monitoring (TDM) will be that it is clinically practical. In this respect, determining plasma or saliva zidovudine parameters is better than intracellular monitoring because of the relative ease of collecting and assaying plasma and saliva specimens. Assaying intracellularly total zidovudine phosphates is technically more attractive than assaying separate phosphates, because no additional separation step is needed.

## 9. Rationale for Individualisation of Zidovudine Therapy

Individualisation of drug therapy based on TDM can in general be an effective means to manage response to drug therapy. The ultimate goal of TDM is to find a balance between maximal efficacy and minimal toxicity of a drug by adjusting the dosage, guided by, for instance, the plasma concentration. To influence efficacy and/or toxicity by adjusting the dosage, a clear pharmacokinetic-pharmacodynamic relationship must be established. Drugs used for life-threatening diseases with a proven pharmacokinetic-pharmacodynamic relationship, a small therapeutic range, large interindividual variation of pharmacokinetic and pharmacodynamic parameters and severe adverse effects are particularly good candidates for TDM.

Taking into account the seriousness of the disease, the adverse effects of the drug and the large interindividual pharmacokinetic variation, zidovudine would seem to be an ideal candidate for TDM. However, the usefulness of the TDM concept has not been demonstrated so far,<sup>[67]</sup> because a clear therapeutic window based on pharmacokinetic-pharmacodynamic relationships has not yet been defined. Moreover, the efficacy of zidovudine is usually determined by measuring surrogate markers instead of primary end-points, thus possibly hampering an adequate estimation. However, several studies indicate that a relationship exists between plasma pharmacokinetics and toxicity. Once this relationship is quantified, adverse reactions to

zidovudine might be prevented by monitoring plasma zidovudine concentrations.

Monitoring intracellular zidovudine pharmacokinetics may prove to be a more successful means to describe pharmacokinetic-pharmacodynamic relationships, especially if no relevant correlation between intra- and extra-cellular zidovudine pharmacokinetic parameters should exist. Monitoring intracellular phosphorylation might be a better way to predict the development of zidovudine-resistant strains than monitoring plasma zidovudine concentrations.<sup>[56]</sup>

Furthermore, owing to the large fluctuations in plasma zidovudine concentrations during 1 dose interval (fast absorption and elimination), concentration monitoring might prove to be impractical.<sup>[67]</sup> During 1 dosage interval, intracellular concentrations of zidovudine anabolites fluctuate much less (larger  $t_{max}$  and larger  $t_{1/2}$ ) and, although technically more difficult to assay, might therefore be much more promising for zidovudine monitoring in practice.

The large interindividual variation in zidovudine pharmacokinetics calls for individualisation of therapy. Determination of zidovudine pharmacokinetic-pharmacodynamic relationships, however, is needed first, in order to determine the relevance of the observed interindividual pharmacokinetic differences. Once these goals have been achieved, the relevance of pharmacokinetic or pharmacodynamic interactions between zidovudine and other drugs can be evaluated. Subsequently, it might become possible to rationally individualise zidovudine therapy and assure maximal efficacy and minimal toxicity for patients using zidovudine.

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