

# Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in patients with the acquired immunodeficiency syndrome

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- 1 Zidovudine (ZDV) has proved unsuccessful in controlling disease progression over extended periods of time in patients with AIDS. Combination of ZDV with another reverse transcriptase inhibitor, dideoxyinosine (ddI) may improve the duration of effectiveness of antiretroviral therapy. The aim of this study was to investigate the possibility of a pharmacokinetic drug interaction between ZDV and ddI.
- 2 The pharmacokinetics of ZDV and ddI were determined in eight patients with AIDS who were randomised to receive ZDV 250 mg orally, ddI 250 mg orally or a combination of ZDV 250 mg plus ddI 250 mg orally on 3 study days separated by 1 week.
- 3 The administration of ZDV did not significantly alter ddI pharmacokinetics. The mean AUC was  $6.8 \pm 2.0$  s.d. and  $7.6 \pm 2.5$  s.d.  $\mu\text{mol l}^{-1} \text{h}$  and oral clearance was  $2766 \pm 686$  and  $2660 \pm 1297$   $\text{ml min}^{-1}$  in the presence and absence of ZDV, respectively.
- 4 In the presence of ddI the elimination half-life of ZDV was increased significantly by 18% from  $1.1 \pm 0.3$  to  $1.3 \pm 0.3$  h ( $P < 0.05$ ) and the mean AUC increased significantly by 35% from  $4.8 \pm 1.5$  to  $6.5 \pm 1.5$   $\mu\text{mol l}^{-1} \text{h}$  ( $P < 0.05$ ). The clearance was decreased by 29% from  $3518 \pm 1123$  to  $2505 \pm 575$   $\text{ml min}^{-1}$ , but this difference was not significant. The renal clearance of ZDV was not altered by ddI.
- 5 Administration of ddI also resulted in a significant 22% increase in the AUC of GZDV, from  $28.5 \pm 15.7$  to  $34.9 \pm 12.8$   $\mu\text{mol l}^{-1} \text{h}$  ( $P < 0.05$ ).
- 6 Combination therapy with the nucleoside analogues ZDV and ddI may be the way forward in the treatment of advanced HIV disease, but the pharmacokinetic drug interaction described here should be taken into consideration.

**Keywords** zidovudine dideoxyinosine pharmacokinetics

## Introduction

Zidovudine (3'-azido-3'-deoxythymidine; ZDV) a thymidine analogue antiretroviral drug inhibits human immunodeficiency virus (HIV) replication, reducing mortality and the frequency of opportunistic infections when administered to patients with the acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC) [1]. However, ZDV has proved unsuccessful in controlling disease progression over extended periods of time and viral isolates with

diminished *in vitro* sensitivity have emerged following ZDV treatment [2, 3]. Several strategies have been suggested to improve the duration of effectiveness of antiretroviral therapy including the combination of ZDV and another reverse transcriptase inhibitor, dideoxyinosine (ddI), as ZDV resistant isolates do not exhibit cross resistance to ddI [4]. A preliminary study suggested that simultaneous therapy with ZDV and ddI leads to significantly greater and

more sustained improvement in CD4 (helper) T-lymphocyte counts and weight gain. Although lower doses of each nucleoside analogue were used in the simultaneous-therapy regimen, the incidence of drug toxicity appeared to be higher thus raising the possibility of drug interaction [5, 6]. This was not confirmed by a subsequent study of combination therapy with variable doses of ZDV and ddI [7].

The bioavailability of ZDV is variable and approaches 65%. The mean volume of distribution is  $1.4 \text{ l kg}^{-1}$  with plasma protein binding less than 25%. The drug has an elimination half-life of approximately 1 h and is metabolised extensively to an ether glucuronide 3'-azido-3'-deoxy-5'- $\beta$ -D-glucopyranuronosylthymidine (GZDV) [8]. Following an oral dose 75% of the drug is recovered in the urine as GZDV with 15% as unchanged drug. A small percentage of ZDV (< 5%) is phosphorylated intracellularly to the active moiety ZDV triphosphate which inhibits viral reverse transcriptase [9]. Since ddI is acid labile it is administered in a buffered solution with a mean bioavailability of 35%. In addition to intracellular formation of dideoxyadenosine triphosphate (ddA-TP), ddI is also broken down to hypoxanthine and uric acid. The elimination half-life following oral administration ranges from 0.6 to 1.3 h with a clearance of  $1.0 \text{ l kg}^{-1} \text{ h}^{-1}$  [10]. In this study we investigated the pharmacokinetics of ZDV and ddI when administered alone and in combination to patients with AIDS.

## Methods

### Patients

Eight male patients, aged 32 to 48 years, with sexually acquired HIV infection participated in this study. All patients had AIDS according to the revised CDC definition [11]. Three patients had previous *Pneumocystis carinii* pneumonia (PCP), one had cytomegalovirus (CMV) retinitis and one had cryptosporidiosis (CDC Group IV C<sub>1</sub>). Two patients had recurrent oral candidiasis (CDC Group IV C<sub>2</sub>). The AIDS defining illness in the remaining patient was Kaposi's sarcoma (CDC Group IV D). The average CD4 count was  $75 \times 10^6 \text{ l}^{-1}$  indicating significant immunosuppression. All patients had normal liver function as assessed by the Pugh classification (Pugh score < 5) [12]. Values of urea and creatinine were in the normal range indicating no evidence of renal dysfunction. Current medications included ZDV, 250 mg twice daily and PCP prophylaxis with cotrimoxazole, 960 mg daily in all patients, i.v. ganciclovir  $5 \text{ mg kg}^{-1} \text{ day}^{-1}$  in the patient with CMV retinitis and twice monthly i.v. liposomal doxorubicin  $20 \text{ mg kg}^{-1} \text{ m}^{-2}$  for the patient with Kaposi's sarcoma. Patients did not receive medication known to interfere with ZDV or ddI pharmacokinetics. Approval for the study was obtained from the local Ethics Committee and each patient provided written informed consent.

### Protocol

Eight patients were studied on three occasions separated by at least 1 week. Patients were randomised to receive ZDV 250 mg orally, ddI 250 mg sachet orally or a combination of ZDV 250 mg plus ddI 250 mg sachet. Patients were advised to take their usual medications except on the study days. On each study day patients attended following an overnight fast from 00.00 h. An indwelling intravenous cannula was inserted in the cubital fossa for blood sampling. ZDV 250 mg, ddI 250 mg sachet or a combination of ZDV 250 mg plus ddI 250 mg were administered at 09.00 h and blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5 and 6 h. Urine samples were collected over the 6 h study period. All samples were centrifuged immediately to minimise the metabolism of ddI by erythrocytes [13]. The separated plasma was then heated at 58° C for at least 30 min in a waterbath to inactivate the AIDS virus [14]. Preliminary studies indicated that heating had no effect on drug analysis.

### Drug analysis

ZDV and its glucuronide metabolite (GZDV) were measured in plasma and urine by high performance liquid chromatography (h.p.l.c.) as reported previously [15]. Plasma samples were spiked with  $5 \mu\text{M}$  of A22U (Wellcome, Beckenham) as internal standard and were ultrafiltered using an Amicon Centrifree Micropartition System. The ultrafiltrates were analysed subsequently by h.p.l.c.. Samples were eluted on an Ultratech 50DS column ( $4.6 \times 250 \text{ mm}$ ) using a mobile phase of 25 mM ammonium phosphate buffer, pH 7.2, with a linear gradient of 0–30% v/v acetonitrile over 35 min followed by a return to 100% buffer over 5 min and a 5 min re-equilibration period with 100% buffer at a flow rate of  $0.6 \text{ ml min}^{-1}$ . Retention times of authentic standards (u.v. detection at 267 nm) were 19, 26 and 28 min for GZDV (Wellcome, Beckenham), A22U and ZDV (Wellcome, Beckenham), respectively. Peak height ratios of ZDV and GZDV to the internal standard were used to calculate concentrations from standard curves (range 0–20  $\mu\text{M}$  and 0–40  $\mu\text{M}$  for ZDV and GZDV, respectively). Intra-assay coefficients of variation were 8.1%, 1.7% and 2.1% for 0.25, 2.5 and 20  $\mu\text{M}$  ZDV, respectively and 8.3%, 5.9% and 3.2% for 0.5, 5.0 and 40  $\mu\text{M}$  GZDV, respectively ( $n = 10$ ). Interassay coefficients of variation were 5.7% and 7.9% for 2.5  $\mu\text{M}$  ZDV and 5  $\mu\text{M}$  GZDV, respectively ( $n = 5$ ). Urine samples were diluted 1:100, spiked with  $5 \mu\text{M}$  of internal standard (A22U) and analysed by h.p.l.c. as above. Intra-assay coefficients of variation were 5.2% and 5.1% for 0.5 and 20  $\mu\text{M}$  ZDV, respectively, and 8.7% and 9.6% for 1.0 and 40  $\mu\text{M}$  GZDV, respectively ( $n = 10$ ). Interassay coefficients of variation were 9.9% and 9.8% for 2.5  $\mu\text{M}$  ZDV and 5  $\mu\text{M}$  GZDV, respectively ( $n = 5$ ). The assays had a limit of detection of 0.1  $\mu\text{M}$  for ZDV and 0.2  $\mu\text{M}$  for GZDV.

For the assay of ddI, plasma was diluted 1:100 with blank plasma and mixed for 10 min. Aliquots of

plasma were analysed using a commercially available radio-immunoassay kit (Sigma) with the method being modified to reduce volumes of the reagents, but with all other procedures remaining as given in the kit. In brief, 3.5 nCi [<sup>3</sup>H]-ddI and rabbit anti-ddI antiserum were added to aliquots of diluted plasma and incubated at room temperature for 1 h. Immunoprecipitation reagent (anti-rabbit IgG antiserum) was added and the tubes were centrifuged (2000 g, 15 min 4° C). The supernatant was discarded and the pellet was redissolved in 0.1N hydrochloric acid. Aliquots of the dissolved pellet were subjected to radiometric analysis. Intra-assay coefficients of variation were 12.3% and 13.7% for 0.4 and 1.06 µM ddI, respectively (n = 10). At the same concentrations inter-assay coefficients of variation were 14.3% and 15.1% (n = 48). The assay had a limit of detection of 0.01 µM.

Data analysis

Values of C<sub>max</sub> (µmol l<sup>-1</sup>) and t<sub>max</sub> (h) were determined for ZDV, GZDV and ddI directly from the data. The elimination rate constant (λ<sub>z</sub>) was calculated by linear regression of the terminal portion of the log plasma drug concentration-time curve using the method of least squares. The terminal elimination half-life (t<sub>1/2,z</sub>) was calculated from ln 2/λ<sub>z</sub>. AUC values for ZDV, GZDV and ddI were calculated using the linear trapezoidal rule with extrapolation from the last data point to infinity using C<sub>(last)</sub>/λ<sub>z</sub> (the mean percentage of area that was extrapolated was 5.4% for ZDV, 2.3% for GZDV and 5.0% for ddI). The oral clearance (CL<sub>o</sub>) of ZDV and ddI was calculated from Dose/AUC. The renal clearance (CL<sub>R</sub>) of ZDV was calculated from the ratio of the amount recovered in urine to plasma AUC determined over equal periods of time. Complete urine collections were only obtained from five patients.

We assumed that a 30% change in AUC would be clinically significant and performed a power analysis using known coefficients of variation from a previous study [15]. This indicated that eight subjects should be sufficient to detect such a change (significance level of α = 0.05 and a power of 1-β = 0.9).

Differences in kinetic parameters between the treatments were compared using Student's two-tailed paired t-test. A P value of < 0.05 was considered statistically significant.

Table 1 Pharmacokinetic parameters for ZDV and GZDV following oral administration of ZDV (250 mg) alone or in combination with orally administered ddI (250 mg) to eight HIV-positive patients. Data expressed as mean ± s.d. with the exception of t<sub>max</sub>, median (range). 95% CI: 95% confidence intervals of the differences between the means for the two regimens, P-value: probability of a difference between the two regimens calculated using Student's t-test for paired data

|                                           | ZDV parameters |            |         | GZDV parameters |             |               |
|-------------------------------------------|----------------|------------|---------|-----------------|-------------|---------------|
|                                           | ZDV alone      | ZDV + ddl  | P value | ZDV alone       | ZDV + ddl   | P value       |
| C <sub>max</sub> (µmol l <sup>-1</sup> )  | 4.3 ± 2.8      | 6.5 ± 4.7  | 0.352   | 15.1 ± 5.8      | 18.8 ± 6.4  | 0.155         |
| t <sub>max</sub> (h)                      | 1.0            | 0.75       | —       | 1.25            | 1.0         | —             |
| t <sub>1/2,z</sub> (h)                    | (0.25-1.75)    | (0.5-1.25) | —       | (0.5-2.0)       | (0.75-3.0)  | —             |
| AUC (µmol l <sup>-1</sup> h)              | 1.1 ± 0.3      | 1.3 ± 0.3  | 0.036*  | 1.0 ± 0.2       | 1.2 ± 0.2   | 0.376         |
| CL <sub>o</sub> (ml min <sup>-1</sup> )   | 4.8 ± 1.5      | 6.5 ± 1.5  | 0.044*  | 28.5 ± 15.7     | 34.9 ± 12.8 | 0.045*        |
| CL <sub>R</sub> † (ml min <sup>-1</sup> ) | 3518 ± 1123    | 2505 ± 575 | 0.074   | —               | —           | —             |
|                                           | 198 ± 75       | 171 ± 130  | 0.441   | —               | —           | —             |
|                                           |                |            |         | 95% CI          |             | 95% CI        |
|                                           |                |            |         | -7.25, 2.95     |             | -9.18, 1.79   |
|                                           |                |            |         | —               |             | —             |
|                                           |                |            |         | -0.47, -0.02    |             | -0.37, 0.16   |
|                                           |                |            |         | -3.34, -0.06    |             | -12.54, -0.19 |
|                                           |                |            |         | -128, 2153      |             | —             |
|                                           |                |            |         | -60.2, 113.8    |             | —             |

†Data from five patients only.

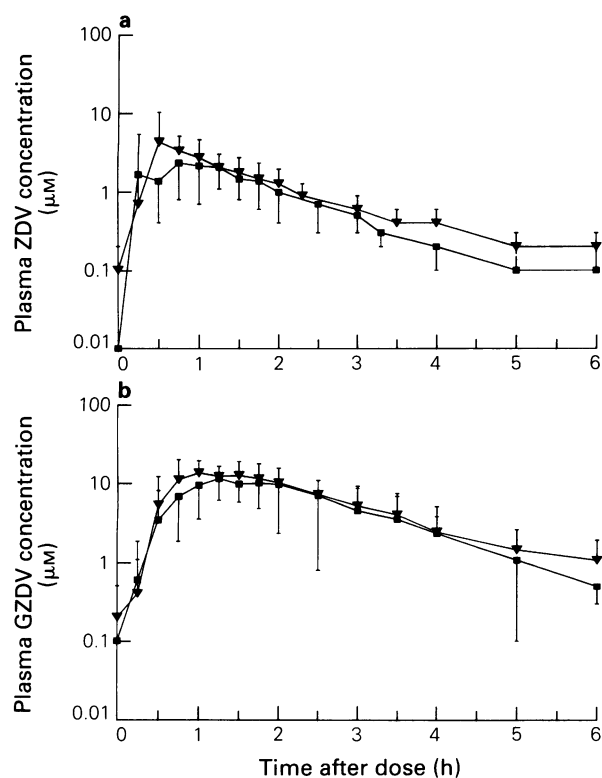
\*Statistically significant difference between the two regimens, P < 0.05.

Results

ZDV kinetics

The pharmacokinetic parameters of ZDV in the presence and absence of ddI are shown in Table 1. Values of the maximum plasma concentration (C<sub>max</sub>) and time to maximum concentration (t<sub>max</sub>) were consistent with those reported in previous studies [8, 15]. In the presence of ddI the terminal elimination half-life of ZDV was increased significantly by 18% (1.1

± 0.3 to 1.3 ± 0.3 h) and the AUC value was increased by 35% (4.8 ± 1.5 to 6.5 ± 1.5 µmol l<sup>-1</sup> h). (Figure 1a). The oral clearance was decreased by 29% in the presence of ddI (3518 ± 1123 to 2505 ± 575 ml min<sup>-1</sup>), but this difference was not statistically significant. Renal clearance of ZDV (data from five patients) was not altered by ddI.



**Figure 1** Mean plasma ZDV (a) and GZDV (b) concentrations ( $\pm$  s.d.) in eight HIV-positive patients following oral administration of ZDV (250 mg) alone (■) or in combination (▼) with orally administered ddI (250 mg).

#### GZDV kinetics

There was no significant difference between  $t_{\max}$ ,  $C_{\max}$  and  $t_{1/2,z}$  of GZDV in the presence and absence of ddI (Table 1). However, the AUC for GZDV was increased significantly by 22% ( $28.5 \pm 15.7$  to  $34.9 \pm 12.8 \mu\text{mol l}^{-1} \text{h}$ ) in the presence of ddI (Figure 1b).

#### ddI kinetics

The pharmacokinetic parameters for ddI in the presence and absence of ZDV are shown in Table 2. Administration of ZDV did not alter ddI kinetics significantly. Mean AUC values were  $7.6 \pm 2.5$  and  $6.8 \pm 2.0 \mu\text{mol l}^{-1} \text{h}$  and oral clearances were  $2660 \pm 1297$  and  $2766 \pm 686 \text{ ml min}^{-1}$  without and with ZDV, respectively (Figure 2).

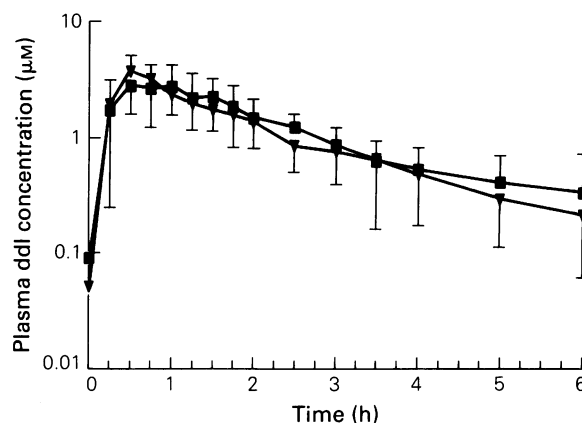
#### Discussion

The complexity of the HIV life cycle and the ability of the virus to mutate suggests that monotherapy with the nucleoside analogues is unlikely to produce effective pharmacologic suppression of the virus [16]. One strategy involves the combination of antiretroviral agents, and preliminary work with ZDV combined with ddI has been encouraging. As ZDV undergoes extensive hepatic glucuronidation [8] together with minor formation of a reduced metabolite, 3'-amino-

**Table 2** Pharmacokinetic parameters for ddI following oral administration of ddI (250 mg) alone or in combination with orally administered ZDV (250 mg) to eight HIV-positive patients. Data are expressed as mean  $\pm$  s.d. with the exception of  $t_{\max}$ , median (range). 95% CI: confidence intervals of the differences between the means for the two regimens.

|                                            | ddl alone       | ddl + ZDV       | 95% CI      |
|--------------------------------------------|-----------------|-----------------|-------------|
| $C_{\max}$<br>( $\mu\text{mol l}^{-1}$ )   | $3.4 \pm 1.1$   | $3.8 \pm 1.2$   | -1.11, 0.28 |
| $t_{\max}$ (h)                             | 0.75 (0.25–2.5) | 0.50 (0.50–2.0) | —           |
| $t_{1/2,z}$ (h)                            | $1.2 \pm 0.3$   | $1.3 \pm 0.2$   | -0.25, 0.18 |
| AUC<br>( $\mu\text{mol l}^{-1} \text{h}$ ) | $7.6 \pm 2.5$   | $6.8 \pm 2.0$   | -0.50, 2.15 |
| $CL_o$<br>( $\text{ml min}^{-1}$ )         | $2660 \pm 1297$ | $2766 \pm 686$  | -962, 751   |

Note: One patient was excluded from the calculation of  $t_{1/2,z}$ , AUC and  $CL_o$  because the AUC from the last data point ( $t = 6$ ) to infinity was greater than 15%. There were no significant differences in any parameters.



**Figure 2** Mean plasma ddI concentrations ( $\pm$  s.d.) in eight HIV-positive patients following oral administration of ddI (250 mg) alone (■) or in combination (▼) with orally administered ZDV (250 mg).

deoxythymidine (AMT, [17]) and ddI is catabolized by purine nucleoside phosphorylase (PNP) to hypoxanthine and uric acid [13], a metabolic drug interaction would seem unlikely. Previously we have investigated the effects of a number of drugs, including ddI, on ZDV glucuronidation *in vitro* using human liver microsomes. In the *in vitro* study ddI failed to inhibit ZDV glucuronidation at concentrations up to 10 mM [18]. This is supported by a study in rats in which ZDV and ddI were administered by intravenous injection alone and in combination. There was no alteration in kinetic parameters for either drug on coadministration [19]. However, studies conducted in monkeys, an animal that serves as an appropriate model for the pharmacokinetics of both ZDV and ddI in humans, suggest that a drug interaction may occur. When zidovudine was administered intravenously to nine monkeys in doses giving plasma drug concentrations ranging from 4 to 11  $\mu\text{g ml}^{-1}$  there was no alteration in the kinetics of ddI which was also ad-

ministered intravenously at a dose of 20 mg kg<sup>-1</sup> [20]. However, another study in monkeys investigated the pharmacokinetics of ZDV administered intragastrically at a dose of 20 mg kg<sup>-1</sup> in the presence and absence of ddI. The authors concluded that there was evidence to suggest that both renal and metabolic elimination of ZDV and renal elimination of GAZT may be inhibited by ddI [21].

In this study of eight patients with AIDS, administration of ZDV 250 mg orally did not interfere with ddI kinetics. However, ingestion of a 250 mg sachet ddI did result in an 18% increase in ZDV half-life together with a 35% increase in AUC. One explanation for the increase in plasma concentrations of ZDV is inhibition of metabolic clearance, which would be consistent with animal studies but contrary to the *in vitro* findings in human liver. Another possible mechanism for the increased AUC of ZDV and GZDV is an alteration in ZDV absorption. Coadministration of ddI has resulted in altered absorption of other drugs such as dapsone [22]; an alteration in gastric pH due to the citrate buffer present in the ddI sachet being the postulated mechanism. As ZDV was administered orally in the present study it was not possible to assess its absorption. Although the increased AUC for GZDV could be due, in part, to increased absorption of ZDV in the presence of ddI, a decrease in renal elimination of GZDV cannot be excluded. There was no decrease in the renal clearance of ZDV in the presence of ddI. Therefore, as in animal studies, the changes in the kinetic parameters of ZDV may reflect a number of underlying mechanisms, i.e. altered absorption, a decreased metabolic clearance of ZDV and a decrease in the renal elimination of GZDV.

The clinical implications of a 30% increase in plasma concentrations of ZDV when coadministered with ddI are unclear, although the obvious concern is an increase in toxicity. In one pharmacokinetic study toxicity was associated with an increased AUC in

patients treated with ZDV 200 mg four hourly [23]. The mean trough drug concentrations were also greater in patients demonstrating toxic effects. This is consistent with findings of pharmacokinetic studies of ZDV in children with symptomatic HIV infection. Steady state plasma concentrations of ZDV were found to be higher in children who developed severe neutropenia (neutrophils < 0.5 × 10<sup>9</sup> l<sup>-1</sup>) compared with children who did not develop haematological toxicity [24]. In the majority of children with neutropenia the steady state plasma concentration of ZDV was greater than 3.0 μmol l<sup>-1</sup>. However, in a recent comparative study of HIV-positive patients with and without ZDV-induced bone marrow aplasia/hypoplasia there was no indication that ZDV haematological toxicity was directly related to plasma concentrations of the drug [25]. Therefore, the clinical implications of the alterations in ZDV kinetics described are unclear. However, haematological toxicity is more frequent in patients with advanced disease, and these are the patients for whom combination therapy is being considered.

Our findings are in contrast to those of Collier *et al.* [7] who failed to demonstrate a pharmacokinetic drug interaction or increased drug toxicity in patients administered ZDV and ddI in combination. However, the patients in their study were heterogeneous with respect to risk factors for HIV (15% were intravenous drug users), were less immunosuppressed (> 50% were asymptomatic and only 15% with AIDS) with a mean CD4 count of 259 × 10<sup>6</sup> l<sup>-1</sup> (compared with 75 × 10<sup>6</sup> l<sup>-1</sup> in our study) and received lower doses of ZDV and ddI.

Combination therapy with the nucleoside analogues ZDV and ddI may be the way forward in the treatment of advanced HIV disease, but the pharmacokinetic drug interaction described here should be taken into consideration.

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