PHARMACOKINETICS OF ZIDOVUDINE DOSED TWICE-DAILY ACCORDING TO WHO WEIGHT-BANDS IN AFRICAN HIV-1-INFECTED CHILDREN

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ABSTRACT (updated)

Background: Although zidovudine (ZDV) is widely used in children, pharmacokinetic (PK) data, particularly on the most commonly used twice daily regimens and WHO-recommended weight-band dosing, are scarce.

Methods: Two intensive PK crossover studies were undertaken in HIV-1-infected Ugandan children in the ARROW trial with samples 0, 1, 2, 4, 6, 8, and 12 hours after observed intake of ZDV at steady-state (with other ART). Dosing followed WHO guidelines: 100/120mg am and pm ZDV as syrups for 10-12/12-15kg; 150/300mg am and pm ZDV as Combivir (CBV) tablets for 12-20/30-35kg, and 300mg am, 150mg pm for 20-30kg. The original PK studies had compared twice-daily syrups vs twice-daily tablets, and twice- to once-daily lamivudine+abacavir (some children also took ZDV at the first PK day). In exploratory analyses, associations between ZDV AUC_{0-12} and sex, age, dose(mg/m^2), weight- and height-for-age, and formulation were investigated using multivariable mixed models allowing for multiple AUC_{0-12} per child.

Results: 45 children had 1 or 2 ZDV AUC_{0-12}: 17 (3-12 years) once on tablets and 28 (1-4 years) once on syrups and once on tablets 4 weeks later. 8 children were on tablets in the 20-30kg split dose weight-band and 17 (38%) were boys. Median (IQR) age at the first PK day was 3.4 (2.6-6.2) years. One PK with implausible time-concentration curve was excluding, leaving 72 PK curves in analysis with median ZDV dose 242 (214-278) mg/m^2. Overall median (IQR) AUC_{0-12} was 3.19 (2.23-4.02) h.mg/L (n=72), 32% higher than reported for adults (mean 2.4 h.mg/L SPC CBV). ZDV AUC_{0-12} was 0.41 h.mg/L higher for every 50mg/m^2 higher ZDV dose [95% CI 0.12,0.69] (p=0.005). Associations between age and ZDV AUC_{0-12} varied across the age range (non-linearity p=0.002). ZDV AUC_{0-12} was 1.05 h.mg/L lower per year older up to 4 years of age [0.46,1.65] (p<0.001): over 4, there was no association with age (+0.04 h.mg/L per year older [-0.15,+0.23], p=0.72). ZDV AUC_{0-12} was 0.75 h.mg/L lower for every unit higher weight-for-age [0.32,1.18] (p=0.001). There was no independent effect of sex (p=0.62), height-for-age (p=0.49) or syrups/tablets (p=0.79). 34 children had haemoglobin values within ±1 day of PK: there was marginal evidence for 0.31 g/dL lower haemoglobin per 1 h.mg/L higher ZDV AUC_{0-12} [-0.65,+0.03] (p=0.07).

Conclusions: ZDV exposure in children in Africa dosed according to WHO guidelines was on average 32% higher than in adults. Exposure appeared highest in youngest children: further studies of potential mechanisms and associations with clinically relevant toxicity are needed.

Keywords: zidovudine, pharmacokinetics, HIV-1, children, Africa

INTRODUCTION

- WHO guidelines for the treatment of HIV-1 infected children recommend two nucleoside reverse transcriptase inhibitors (NRTIs) as part of combination treatment of first line therapy[1]
- For infants and children, the current WHO-preferred nucleoside backbone for an ART regimen is lamivudine (3TC) + zidovudine (ZDV)[1], taking into consideration toxicity profiles and costs
  - ZDV+3TC is also available as a scored adult tablet, Combivir (CBV), which can be split for paediatric dosing
- Until now only little is known about pharmacokinetics of twice-daily ZDV in children, particularly in African children[2]
- In this study we determined whether WHO-recommended weight-band dosing provides optimal ZDV exposure in the target population

METHODS

- 45 HIV-infected Ugandan children aged 1-12 years on ZDV (as syrup or as CBV tablets) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) were included in the ZDV substudy of the ARROW trial (www.arrowtrial.org)[3]
- Children received twice daily ZDV dosed according to WHO recommendations (Table 1) as 100/120 mg syrups or halved or whole 150/300 mg CBV tablets
- The original ARROW PK studies had compared twice-daily syrups vs twice-daily tablets[4], and twice- to once-daily lamivudine+abacavir[5] (some children also took ZDV at the first PK day)
  - Samples were taken t = 0, 1, 2, 4, 6, 8 and 12 hours after observed intake of ART
  - In the first study, children switching from syrups to tablets had a PK day on ZDV syrups, then switched to CBV tablets. PK sampling was repeated 4 weeks later
  - In the second study, children had an intensive PK day 36 weeks after starting ART with CBV+ABC+EFV. They then dropped ZDV and moved to once daily 3TC+ABC+EFV, with a second PK day 4 weeks later (not included here as children were no longer taking ZDV)
- In exploratory analyses, associations between ZDV AUC_{0-12} and sex, age, dose (mg/m^2), weight- and height-for-age, and formulation were investigated using multivariable mixed models allowing for multiple AUC_{0-12} per child

RESULTS - DEMOGRAPHICS

Table 1: Baseline demographics of ARROW children with full pharmacokinetic curves for ZDV

		Total
Number of children with 1 or 2 evaluable PKs		45
1-4 years; 2PK one on syrups and one on tablets, n (%)		28 (62%)
3-12 years; 1PK on tablets, n (%)		17 (38%)
Male, n (%)		17 (38%)
Age at first PK, years		3.4 (2.6-6.2)
Weight at first PK, kg		12.6 (12.3-18.0)
BSA, m^2		0.56 (0.53-0.71)
Weight-for-age, z-score at first PK		-1.09 (-1.62 to -0.56)
Height-for-age, z score at first PK		-1.85 (-2.68 to -1.20)
Number of evaluable PKs		72
Am ZDV dose at PK visits, mg/m^2		242 (214 to 278)
Total ZDV dose at PK visits, mg/m^2		466 (424 to 546)
100mg BID ZDV syrup, 16.7-20 mg/kg, 386 to 392 mg/m^2	weight-band 10-12 kg, n (%)	8 (11%)
120mg BID ZDV syrup, 16-20 mg/kg, 415 to 481 mg/m^2	weight-band 12-15 kg, n (%)	20 (27%)
150mg BID CBV tablet, 15-20 mg/kg, 365 to 595 mg/m^2	weight-band 15-20 kg, n (%)	36 (50%)
150mg am/300mg pm CBV tablets, 15-22.5 mg/kg, 414 to 564 mg/m^2	weight-band 20-30 kg, n (%)	8 (11%)

Values are n (%) for categorical variables and median (interquartile range, IQR) for continuous variables. Note that some PK days were performed on a dose associated with the previous weight-band: eg a child weighing 11 kg at the last visit and 12kg at the PK day would have had PK performed on 100mg ZDV syrup BD at steady state. These PK evaluations were not included in the previous main study analyses. WHO doses similar but not identical to SPC.

RESULTS - PHARMACOKINETICS 1

Figure 1: mean ZDV plasma concentrations

- T_{max} was at 1 hour in 63 (88%) of curves, and at 2 hours in the remainder

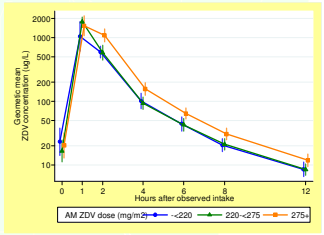


Figure 2: relationship between ZDV exposure (AUC_{0-12h}) and ZDV am dose at PK (mg/m^2)

- Higher doses were associated with higher exposure (adjusted p=0.005)

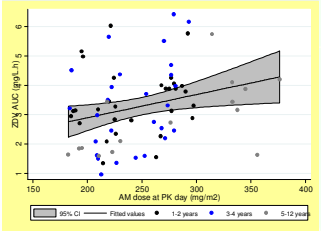
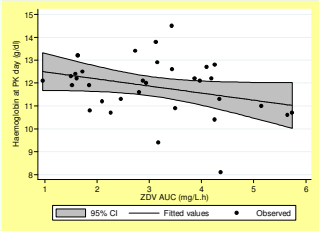


Figure 3: relationship between haemoglobin and ZDV exposure (AUC_{0-12h}) at the PK day

- Higher AUC_{0-12} was marginally associated with lower haemoglobin (p=0.07)



RESULTS - PHARMACOKINETICS 2

- ZDV exposure (AUC) is mainly higher than previously reported in adults[2] (table 2)

Table 2: Pharmacokinetic parameters of ZDV

ZDV	ARROW (n=72)		Lit. data adults[4]
	median (IQR)	mean (CV%)	mean (CV%)
C_{12h} (mg/L)	0.009 [0.006-0.012]	0.011 [66%]	NA
C_{max} (mg/L)	1.83 [1.28-2.31]	1.92 [42%]	2.0 [40%]
AUC_{0-12} (mg/L.h)	3.19 [2.23-4.02]	3.28 [40%]	2.4 [29%]

RESULTS - PHARMACOKINETICS AND ASSOCIATIONS

In multivariable models for ZDV AUC_{0-12}

- ZDV AUC_{0-12} was 0.41 h.mg/L **higher for every 50mg/m^2 higher ZDV dose** [95% CI 0.12,0.69] (p=0.005) (Figure 2) (dose range 183-376 mg/m^2).
- Associations between age and ZDV AUC_{0-12} varied across the age range (non-linearity p=0.002).
  - Independently of the effect of dose, ZDV AUC_{0-12} was 1.05 h.mg/L **lower per year older up to 4 years of age** [0.46,1.65] (p<0.001): **over 4 years of age, there was no association with age** (+0.04 h.mg/L per year older [-0.15,+0.23], p=0.72).
- ZDV AUC_{0-12} was independently 0.75 h.mg/L **lower for every unit higher weight-for-age** [0.32,1.18] (p=0.001) (weight-for-age range -3.4 to +0.8).
- Adjusting for dose, age (as above) and weight-for-age, there was no independent effect of sex (p=0.62), height-for-age (p=0.49) or syrups/tablets (p=0.79).
- 34 children had haemoglobin values within ±1 day of the PK visit: there was marginal evidence for 0.31 g/dL lower haemoglobin per 1 h.mg/L higher ZDV AUC_{0-12} [-0.65,+0.03] (p=0.07) (Figure 3).

CONCLUSIONS

- ZDV exposure (AUC) in children dosed according to WHO weight-bands was on average 32% higher than previously reported in adults
- Exposure appeared higher in younger children and those with greater dose per m^2
- Further studies are needed to explore
  - potential mechanisms, eg reduced clearance vs increased absorption in younger children, using population PK models
  - whether there is any association between higher doses in mg/m^2 and clinically relevant haematological toxicity (eg haemoglobin <7g/dl) in the wider ARROW cohort

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