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P_11

Pharmacokinetics of Once versus Twice Daily Lamivudine and Abacavir in HIV-1 Infected Ugandan Children in the ARROW trial

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Background

- Simplification of antiretroviral (ART) regimens is necessary to help maintain high adherence/acceptability and allow successful long term outcomes
- It has been shown that once daily use of Lamivudine (3TC) and Abacavir (ABC) is feasible in HIV infected European children[1,2] and in adults[3]
- There are no data on once daily use of 3TC and ABC in children in resource-limited settings
- **Objective: to compare the plasma pharmacokinetics (PK) of once versus twice daily 3TC and ABC in HIV-1 infected children in Uganda using weightband based dosing**

Methods

- ARROW is a randomised trial of monitoring and first-line induction-maintenance strategies in 1207 ART-naïve children
- Scored tablets of Combivir (CBV), 3TC and ABC are being used in ARROW allowing greater accuracy of division and improving dosing flexibility
- A subset of 41 children aged 3-12 years on combination ART with 3TC + ABC twice daily were enrolled to this cross-over PK study
- Total daily doses were 150+300mg, 225+450mg and 225/300+600mg for 3TC & ABC respectively in the 12-20kg, 20-25kg & >25kg weightbands respectively
  - —Children weighing 12-20kg took half tablets am and pm; those weighing 20-25kg took a whole tablet am and half a tablet pm, and those weighing 25-30kg took a tablet of ABC am and pm, a tablet of 3TC am and pm or a tablet of combivir am and half pm
- At the end of the induction phase (twice daily dosing to week 36) of ARROW, children had PK samples collected pre-dose, 1, 2, 4, 6, 8 & 12 hrs post dose
- Children were then switched to 3TC + ABC once daily and PK sampling was repeated 4 weeks later with an additional blood draw at 24 hrs post dose
- Daily area under the curve (AUC_{0-24}) and peak level (C_{max}) were compared by geometric mean ratios (GMR)
- A GMR with 90% CI falling within 0.80-1.25 was considered as bioequivalent
- An acceptability questionnaire was administered at the time of switch to once daily and again 4 weeks after switch

Results

- 18 children were aged 3-6 years and 23 aged 7-12 years; 17 (41%) were male
- 23 (56%), 14 (34%) & 4 were in the 12-20kg, 20-25kg & >25kg weightband respectively
- Exclusions: —2 children changed weightband and dose between PK days (protocol exclusion)
  - —4 children were excluded from the lamivudine analysis and 3 children were excluded from the abacavir analysis because of suspected dosing irregularities

Table 1: Pharmacokinetic parameters of lamivudine & abacavir (*all ages combined)

	Lamivudine n = 35 (17 3-6yrs; 18 7-12 yrs)			Abacavir n = 36 (17 3-6 yrs; 19 7-12 yrs)		
	Twice daily geometric mean [%CV]	**Once daily geometric mean [%CV]**	**GMR (once vs twice daily) (90% CI)**	**Twice daily geometric mean [%CV]**	**Once daily geometric mean [%CV]**	**GMR (once vs twice daily) (90% CI)**
AUC_{0-24} µg.h/ml*	12.0 [33%]	13.0 [41%]	1.09 (0.98-1.20)	15.6 [40%]	15.3 [42%]	0.98 (0.89-1.08)
3-6 yrs	11.1 [29%]	12.3 [36%]	1.10 (0.98-1.25)	15.6 [41%]	15.0 [40%]	0.96 (0.87-1.06)
7-12 yrs	12.8 [36%]	13.7 [46%]	1.07 (0.90-1.27)	15.6 [39%]	15.6 [45%]	0.99 (0.84-1.19)
C_{max} µg/ml*	1.8 [38%]	3.2 [42%]	1.76 (1.58-1.96)	4.2 [38%]	6.8 [45%]	1.64 (1.43-1.88)
3-6 yrs	1.7 [44%]	3.0 [35%]	1.78 (1.50-2.11)	4.1 [38%]	6.8 [35%]	1.66 (1.39-1.99)
7-12 yrs	1.9 [32%]	3.3 [48%]	1.75 (1.51-2.02)	4.2 [39%]	6.9 [53%]	1.62 (1.30-2.01)

- AUC_{0-24} of once daily dosing was equivalent to twice daily dosing overall for both 3TC and ABC and when adjusted for age group for ABC (see table 1)
- Overall, C_{max} values for once-daily regimens were 76% and 64% higher than twice daily regimens for lamivudine and abacavir respectively
- No child discontinued once-daily dosing for adverse events and no grade 3/4 adverse event was reported after switch to once daily dosing
  - —No AEs in 2 exclusions with increased 3TC dose due to switching CBV for single 3TC in 25-30kg weightband at end of induction-maintenance strategy (as per WHO dosing)
- In contrast to PENTA 13, 3TC AUC on once daily and twice daily were similar in 3-6 and 7-12 year olds, and similar to levels in older children in PENTA 13. Of note, many younger children in PENTA 13 (whose 3TC levels were lower) were taking syrups whereas all children in ARROW were taking tablets (some divided)

Figure 1: Lamivudine time-concentration profile (µg/ml)

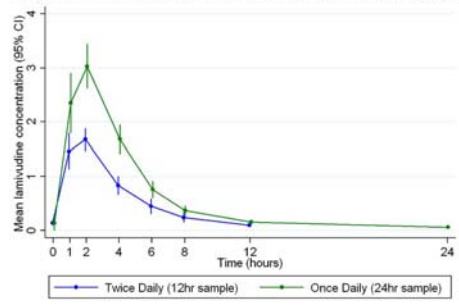
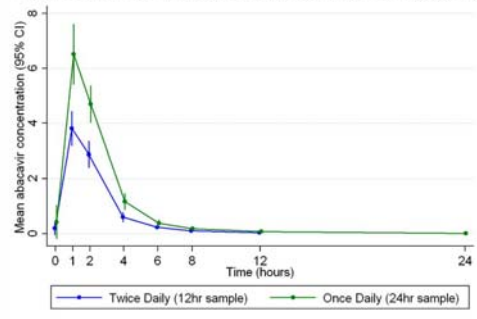


Figure 2: Abacavir time-concentration profile (µg/ml)



- Acceptability:
  - —39/41 (95%) caregivers and 36 (88%) children thought once daily was a lot easier after switching
  - —34/41 (83%) preferred once daily dosing in the morning compared to 7 (17%) who preferred once daily evening dosing

Conclusions

- **In children aged 3-12 years, AUC_{0-24} of both 3TC and ABC were bioequivalent on once and twice daily regimens, whereas C_{max} for once daily regimen was 76% and 64% higher for lamivudine and abacavir respectively**
- **Acceptability of once daily regimens in these ARROW children was very high, and preferred over twice daily**
- **These results suggest feasibility of once daily use of Lamivudine and Abacavir in HIV-infected children in resource-limited settings**
- **Children will continue to be followed on once daily dosing as part of the main ARROW trial for safety and efficacy**
- **Further randomised investigation of the effect of once daily dosing on virological suppression and adherence is planned**

References: **1.** Bergshoeff A, Burger D, Verweij C, Farrelly L, Flynn J, Le Prevost M, Walker S, Novelli V, Lyall H, Khoo S & Gibb D. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther* 2005; 10:239-246. **2.** Jacqz-Aigrain E et al. Plasma pharmacokinetics study of once versus twice daily abacavir and lamivudine as part of combination antiretroviral therapy in HIV-1 infected children aged 3 to 36months. CROI 2009, Poster S-154 . **3.** Moyle GJ, Dejesus E, Cahn P, Castillo SA, Zhao H, Gordon DN, Craig C, Scott TR for the Ziagen Once-Daily in Antiretroviral Combination Therapy (CNA30021) study team. Abacavir Once or Twice Daily Combined With Once-Daily Lamivudine and Efavirenz for the Treatment of Antiretroviral-Naive HIV-Infected Adults: Results of the Ziagen Once Daily in Antiretroviral Combination Study" J Acquir Immune Defic Syndr. 2005 Apr 1; 38(4): 417-42

COLLABORATORS and ACKNOWLEDGEMENTS

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