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PHARMACOKINETICS OF LAMIVUDINE, ABACAVIR AND ZIDOVUDINE ADMINISTERED TWICE-DAILY AS SYRUPS VERSUS SCORED TABLETS IN HIV-1 INFECTED UGANDAN CHILDREN

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BACKROUND

Currently there is an effort to develop simple, more convenient antiretroviral regimens for children to reduce costs and promote adherence. We compared the plasma pharmacokinetics (PK) of lamivudine (3TC), abacavir (ABC) and zidovudine (ZDV) taken twice daily as syrups versus scored tablets in HIV-1 infected Ugandan children.

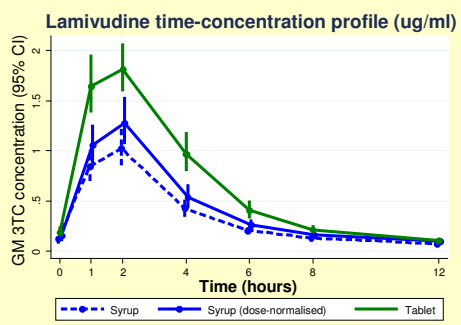
METHODS

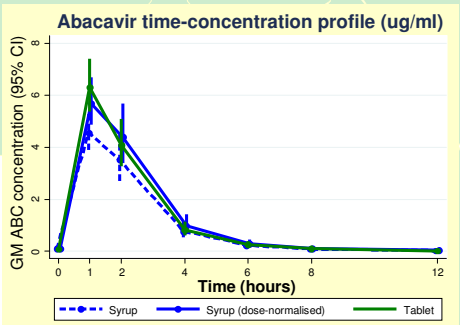
- Eligible children were from 2 Ugandan centres in the ARROW trial, weighing 12-15kg, had taken ZDV, 3TC and ABC syrups twice daily for at least 24 weeks, and were ready to switch from syrups to scored tablets
- Children were expected to remain in the 12-15kg weight band for the next 4 weeks. Those with illnesses affecting PK (e.g., severe diarrhea, vomiting) as well as those who missed any dose in the 3 days before sampling were excluded
- Blood samples were collected at 0, 1, 2, 4, 6, 8 and 12 hours after the child's last morning dose on syrups (observed) prior to switching to scored tablets of Combivir (ZDV+3TC) and ABC. PK sampling was repeated 4 weeks later
- Adjusted Geometric Mean Ratios (aGMR) were calculated to compare plasma area under the curve (AUC0-12) and peak concentrations (Cmax) between tablets versus syrup

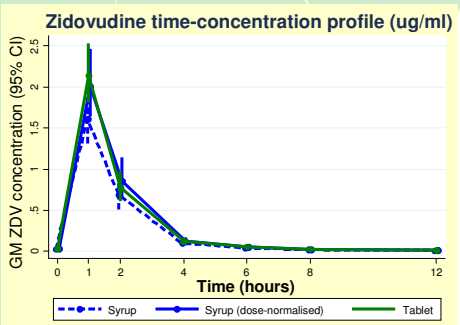
Table 1

Baseline characteristics (n=19)	Median (IQR) or n(%)
Age, years	3.07 (2.39, 3.37)
Gender, male (%)	6 (32%)
Body weight, kg	12.5 (12.2, 12.5)
Weight-for-age z-score (WHO)	-0.89 (-1.26, -0.29)
Height-for-age z-score (WHO)	-2.05 (-3.18, -1.37)
3TC, ABC, ZDV	16 (84%)
3TC, ABC, ZDV, NVP*	3 (16%)
Taking cotrimoxazole prophylaxis**	18 (95%)
WHO weight-band dosing guidelines†	
12-15kg syrup 3TC/ABC/ZDV	60/120/120mg
12-15kg tablet 3TC/ABC/ZDV	75/150/150mg

* all dropped nevirapine after first PK day as part of induction maintaince in the ARROW trial
** one child taking dapsone prophylaxis
† twice-daily







RESULTS

- Following WHO tables, actual doses increased by 25% as children switched from syrups to scored tablets within the 12-15kg weight-band (Table 1), and so PK parameters were normalised to the tablet dose
- **For ZDV and ABC, dose-normalised tablet $AUC_{0\text{-}12}$ and C_{max} were equivalent to syrup, but dose-normalised 3TC exposure was ~55% higher on tablets than on syrups**
- **Actual 3TC exposure on the 75mg tablet dose ($AUC_{0\text{-}12}$ (%CV) 8.2 (20%) h.mg/L) was higher than expected compared to previous paediatric studies, and lower than expected for 60mg syrup dose (4.2 (36%) h.mg/L)**
- There was no evidence of dosing or bio-analytical errors, or problems with administration (vomiting), or with integrity of the product batches, such as degradation

Table 2: Pharmacokinetics of 3TC, ABC & ZDV (n=19)

	syrup GM (95%CI)	syrup aGM (95%CI)	tablet GM (95%CI)	aGMR (90%CI)
3TC				
$AUC_{0\text{-}12}$,mg.h/l	4.16 (3.51, 9.93)	5.20 (4.39, 6.16)	8.20 (7.44, 9.04)	1.58 (1.37, 1.81)
C_{max},mg/l	1.05 (0.88, 1.25)	1.31 (1.10, 1.56)	2.03 (1.83, 2.25)	1.55 (1.33, 1.81)
C_{min}mg/l	0.07 (0.05, 0.09)	0.08 (0.06, 0.11)	0.11 (0.09, 0.12)	1.29 (1.00, 1.66)
CL/F/kg,l/h/kg	1.16 (0.98, 1.37)	1.45 (1.22, 1.71)	0.73 (0.66, 0.80)	0.50 (0.44, 0.58)
ABC				
$AUC_{0\text{-}12}$,mg.h/l	11.85 (9.33, 15.04)	14.81 (11.67, 18.80)	14.32 (11.73, 17.26)	0.96 (0.83, 1.12)
C_{max},mg/l	4.94 (4.10, 5.95)	6.17 (5.13, 7.43)	6.29 (5.37, 7.38)	1.02 (0.89, 1.17)
C_{min}mg/l	0.03 (0.02, 0.05)*	0.04 (0.02, 0.06)*	0.03 (0.02, 0.04)	0.75 (0.52, 1.07)*
CL/F/kg,l/h/kg	0.81 (0.64, 1.03)	1.02 (0.80, 1.29)	0.84 (0.70, 1.01)	0.83 (0.71, 0.96)
ZDV				
$AUC_{0\text{-}12}$,mg.h/l	2.83 (2.26, 3.54)	3.54 (2.83, 4.43)	3.58 (3.02, 4.24)	1.01 (0.87, 1.18)
C_{max},mg/l	1.59 (1.29, 1.96)	1.99 (1.62, 2.45)	2.13 (1.79, 2.52)	1.07 (0.92, 1.25)
C_{min}mg/l	0.01 (0.01, 0.01)**	0.01 (0.01, 0.02)**	0.01 (0.01, 0.10)	0.91 (0.75, 1.11)**
CL/F/kg,l/h/kg	3.54 (2.85, 4.41)	4.43 (3.56, 5.51)	3.35 (2.86, 3.93)	0.75 (0.66, 0.87)

*/** calculated using 17 & 16 detectible values respectively. Adjusted (a)GM and aGMR normalised to tablet doses

DISCUSSION

- **Although ZDV and ABC syrups and tablets gave equivalent exposures, we found higher plasma exposure from twice daily 3TC scored tablets compared to syrups**
- **Further studies to understand the underlying mechanism for differing 3TC exposures from solution and tablets in the target population of HIV-infected children are needed**

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