



# Pharmacokinetics (PK) of Once Daily versus Twice Daily Lamivudine and Abacavir in HIV-1 Infected Children- PENTA 13

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## Introduction

- Simplification of antiretroviral therapy by reducing dosing frequency can enhance compliance to medication in both HIV-1 infected adults and children.
- Very little is known on once daily (q24h) use of nucleoside analogues in HIV-1 infected children.

## Objectives

- To compare the plasma pharmacokinetics (PK) of lamivudine (3TC) 8 mg/kg q24h with 4 mg/kg q12h and of abacavir (ABC) 16 mg/kg q24h with 8 mg/kg q12h.
- To evaluate age-related differences in the PK of these agents.

## Methods

### Study design

- Open label, single sequence, two-period cross-over study
- Children were enrolled 1:1 into age strata of  $\geq 2-6$  and  $>6-13$  years old
- Intensive plasma PK sampling was performed at steady-state during use of 3TC and/or ABC q12h and 4 weeks after switch to q24h
- Plasma concentrations of 3TC and ABC were determined by a validated method of HPLC.
- Non-compartmental PKs were applied. Geometric mean ratios (GMR) with 90% confidence intervals (CI) of PK parameters were calculated to compare q24h and q12h regimens.
- HIV-RNA load measurements were performed at baseline and routinely during the follow-up
- Reported are PK data and a summary of safety and virologic efficacy data up to week 12.

### Inclusion criteria

- age  $\geq 2$ -13 years and confirmed HIV-1 infection
- using combination treatment containing 3TC 4 mg/kg q12h and/or ABC 8 mg/kg q12h; willing to switch 3TC and/or ABC to q24h use
- clinically stable:
- HIV-1 RNA load suppressed, or non-suppressed but relatively low (400-20,000 copies/mL)
- CD4+ cell count stable or rising prior to study entry
- children and/or parents able to give informed consent

### Exclusion criteria

- plasma concentrations of 3TC in HIV-1 infected children (N=19) who used 3TC 4 mg/kg q12h and switched to 8 mg/kg q24h.

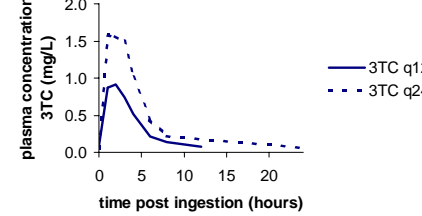


Figure 1B: median plasma concentrations of ABC in HIV-1 infected children (N=14) who used ABC 8 mg/kg q12h and switched to 16 mg/kg q24h.

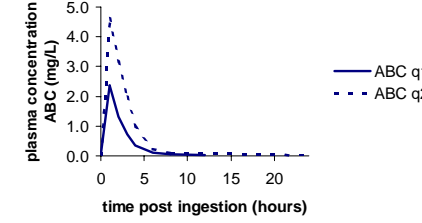


Table 1: PK parameters of 3TC 4 mg/kg q12h and 8 mg/kg q24h and within-patient comparison of q24h vs. q12h

Pharmacokinetic parameter 3TC	4 mg/kg q12h (GM (90% CI)) (N=19)	8 mg/kg q24h (GM (90% CI)) (N=19)	Within-patient comparison (GMR (90% CI)) (N=19)
AUC <sub>0-24</sub> (mg/L*h)	8.88 (7.67-10.28)	9.80 (8.64-11.12)	1.12 (1.03-1.21)
C <sub>max</sub> (mg/L)	1.11 (0.96-1.29)	2.09 (1.80-2.42)	1.90 (1.67-2.16)
C <sub>min</sub> (mg/L)	0.067 (<0.050-0.153)	0.050 (<0.050-0.076)	N.A.*
(median (range))			
Cl/F*kg (L/h*kg)	0.90 (0.78-1.04)	0.80 (0.70-0.92)	0.89 (0.82-0.96)

\*: not available

Table 2: PK of 3TC in children  $\geq 2-6$  vs.  $>6-13$  years old (GM (90% CI))

Pharmacokinetic parameter	3TC 4 mg/kg q12h			3TC 8 mg/kg q24h		
	Children $\geq 2-6$ years old (N=10)	Children $>6-13$ years old (N=9)	P value	Children $\geq 2-6$ years old (N=10)	Children $>6-13$ years old (N=9)	P value
AUC <sub>0-24</sub> (mg/L*h)	7.60 (6.12-9.45)	10.55 (8.82-12.63)	0.050	8.80 (7.43-10.43)	11.04 (9.06-13.45)	0.124
C <sub>max</sub> (mg/L)	0.94 (0.78-1.13)	1.34 (1.08-1.67)	0.033	1.72 (1.48-1.99)	2.59 (2.04-3.28)	0.013
C <sub>min</sub> (mg/L) (median (range))	0.068 (<0.050-0.15)	0.067 (<0.050-0.11)	N.A.*	0.050 (<0.050-0.076)	0.061 (<0.050-0.074)	N.A.*
Cl/F*kg (L/h*kg)	1.09 (0.89-1.34)	0.73 (0.63-0.85)	0.130	0.92 (0.78-1.08)	0.69 (0.55-0.87)	0.069

\*: not available

Table 3: PK parameters of ABC 8 mg/kg q12h and 16 mg/kg q24h and within-patient comparison of q24h vs. q12h

Pharmacokinetic parameter ABC	8 mg/kg q12h (GM (90% CI)) (N=14)	16 mg/kg q24h (GM (90% CI)) (N=14)	Within-patient comparison ABC (GMR (90% CI)) (N=14)
AUC <sub>0-24</sub> (mg/L*h)	9.91 (8.26-11.89)	13.37 (11.80-15.16)	1.35 (1.19-1.54)
C <sub>max</sub> (mg/L)	2.14 (1.79-2.56)	4.80 (4.04-5.71)	2.25 (1.83-2.77)
C <sub>min</sub> (mg/L)	0.025 (<0.015-0.070)	<0.015 (<0.015-0.046)	N.A.*
(median (range))			
Cl/F*kg (L/h*kg)	1.58 (1.30-1.93)	1.16 (1.01-1.34)	0.73 (0.64-0.84)

\*: not available

## Results

### Baseline

- 24 HIV-1 infected children using antiretroviral combination therapy were enrolled; median age (range) 5.6 (2.1-12.8) years; median body weight (range) (22.5 (12.5-60.5) kg
- 20/24 children (10 girls/10 boys) had complete PK data of 3TC (N=19) and/or ABC (N=14)
- One child used amoxicillin/clavulanic acid on the day of PK sampling. Data of this child were not excluded since no interference of the drug with the PK of 3TC nor ABC is expected.
- At baseline, in 16/20 (80%) children, plasma HIV-1 RNA load was <100 copies/mL.

### PK of 3TC (Tables 1 and 2)

- The GMR of AUC<sub>0-24</sub> q24h vs. q12h significantly exceeded 1.0, suggesting non-inferiority in terms of PK of the q24h regimen.
- For C<sub>max</sub> q24h vs. q12h, GMR approximated 2, suggesting linear pharmacokinetics of 3TC.
- Cl/F\*kg was significantly lower for q24h than q12h 3TC.
- No significant differences were found with respect to GMRs between children  $\geq 2-6$  years and children  $>6-13$  years old: GMRs were 1.17 and 1.06 for AUC<sub>0-24</sub>, 1.84 vs. 1.96 for C<sub>max</sub> and 0.85 vs. 0.93 for Cl/F\*kg, respectively (p values all >0.30, data not shown).

### PK of ABC (Tables 3 and 4)

- For C<sub>max</sub> q24h vs. q12h, GMR exceeded 2, suggesting non-inferiority in terms of PK of the q24h with regard to q12h regimen.
- For C<sub>min</sub> q24h vs. q12h, GMR exceeded 2, possibly reflecting more than dose-proportional pharmacokinetics of ABC.
- Cl/F\*kg was significantly lower for q24h versus q12h ABC.
- No difference was found between GMRs in children  $\geq 2-6$  years and children  $>6-13$  years old: GMRs were 1.46 and 1.17 for AUC<sub>0-24</sub>, 2.61 versus 1.72 for C<sub>max</sub> and 0.67 versus 0.85 for Cl/F\*kg, respectively (p values all >0.08, data not shown).
- No significant differences in AUC<sub>0-24</sub>, C<sub>max</sub> and Cl/F\*kg of ABC were observed between children  $\geq 2-6$  years old and children  $>6-13$  years old (Table 4).
- However, in the younger age group, all 9 children using ABC q24h had a C<sub>min</sub> < 0.015 mg/L, vs. 2 out of the 5 older children (p=0.03).
- This finding seems of little clinical relevance due to the long intracellular half-life of ABC's active moiety. For ABC q12h, no such difference seemed present: 1/9 younger children

### Safety

- 15 older children had a C<sub>min</sub> < 0.015 mg/L (p=0.60).
- At week 12 after changing to the q24h regimen, no child had discontinued treatment due to adverse events (AEs).
- One case of grade 3 neutropenia occurred at week 12, which resolved at week 24. This AE was considered possibly drug related

- In none of the patients, changes in clinical chemistry and haematology laboratory measurements were observed after changing 3TC and/or ABC from q12h to q24h.

### Virologic efficacy (week 12)

- 12 weeks after changing to the q24h regimen, HIV-1 RNA load was <100 copies/mL in 17/20 children (85%), while in 3/20 children, HIV-1 RNA loads were 160, 1600 and 3900 copies/mL, respectively.
- Of these 3 children, 2 had already an HIV-1 RNA load >100 copies/mL at baseline (in the 2 other subjects with an HIV-1 RNA load >100 copies/mL at baseline, viral load had become undetectable at the q24h regimen).
- In the 3rd child with HIV-1 RNA load >100 copies/mL, viral load increase was caused by a major compliance problem.

Table 4: PK of ABC in children  $\geq 2-6$  vs.  $>6-13$  years old

Pharmacokinetic parameter	ABC 8 mg/kg q12h			ABC 16 mg/kg q24h		
	Children $\geq 2-6$ years old (N=9)	Children $>6-13$ years old (N=5)	P-value	Children $\geq 2-6$ years old (N=9)	Children $>6-13$ years old (N=5)	P-value
AUC <sub>0-24</sub> (mg/L*h)	9.27 (7.06-12.18)	11.17 (8.76-14.24)	0.408	13.55 (11.19-16.42)	13.06 (10.91-15.63)	0.812
C <sub>max</sub> (mg/L)	1.94 (1.50-2.51)	2.54 (2.00-3.22)	0.215	5.07 (3.92-6.56)	4.36 (3.39-5.60)	0.478
C <sub>min</sub> (mg/L) (median (range))	0.027 (<0.015-0.040)	0.022 (<0.015-0.070)	N.A.*	<0.015 (<0.015-0.015)	0.016 (<0.015-0.046)	N.A.*
Cl/F*kg (L/h*kg)	1.80 (1.37-2.36)	1.26 (0.96-1.64)	0.130	1.21 (1.00-1.47)	1.08 (0.81-1.44)	0.509

\*: not available

## Conclusions

- These PK data, in addition to good 12-week efficacy, and safety suggest feasibility of q24h use of 3TC and ABC in HIV-1 infected children  $\geq 2-13$  years old with suppressed viral load.
- Therapeutic equivalence of q24h regimens of 3TC and ABC should be further evaluated in a comparative clinical trial.
- The tendency for lower plasma levels of 3TC in younger children poses the question, if higher doses of 3TC should be applied in younger children
- Data on intracellular PK may contribute to the evaluation of the clinical relevance of this finding.