



Pharmacokinetics of Abacavir and Lamivudine Once- versus Twice-daily in HIV-infected Thai Children

Passorn Punyahotra, MD

**Infectious Diseases Unit, Department of Pediatrics
Faculty of Medicine, Chulalongkorn University**

Background

- Once daily (OD) dosing: improve adherence
- Abacavir (ABC) and lamivudine (3TC) are approved for OD use in children > 12 years old
- Limited once-daily pharmacokinetic (PK) data of ABC and 3TC in children, especially in Asian

Previous PK studies of ABC and 3TC in European and African children

Studies	ARROW (AVT 2010)	PENTA 13 (AVT 2005)	PENTA 15 (AVT 2010)
Setting	Uganda	Europe	Europe
Age	3-12 years (n=41)	2-13 years (n=14)*	3 to <36 months (n=18)
Age/wt bands	12-<20kg (n=23) 20-<25kg (n=14) ≥25kg (n=4)	2-6 years (n=9) 6-13 years (n=5)	3-<12 months (n=4) 12-<24 months (n=6) 24-<36 months (n=8)
Study design	Twice daily vs. Once daily (PK at 0, 1, 2, 4, 6, 8, 12 hours for twice daily. An additional sample was collected at 24 hours for once daily)		
Conclusion	Similar PK for Twice daily vs. Once daily for both ABC and 3TC		

Musiime V Antivir Ther 2010; 15:1115-1124
PENTA -13. Antivir Ther. 2005;10(2):239-46
PENTA-15. Antivir Ther. 2010;15(3):297-305.

Objective

To describe and compare the PK of once- versus twice-daily ABC and 3TC in HIV-infected Thai children

Hypothesis

Once-daily ABC and 3TC PK parameters are comparable to Twice-daily in HIV-infected Thai children

Bioequivalence of OD and BID: 90% confidence interval (CI) of Geometric mean ratio (GMR) fell between 0.80-1.25

Single-arm, open-label, crossover PK study in 30 Thai children, 3 weight bands

Inclusion criteria

- <18 years, BW \geq 14 kg
- Stable ART, HIV RNA <50 c/ml
- Negative HLA B5701

Exclusion criteria

- Laboratory toxicities \geq gr II
- Active OI
- <80% adherence by pill count

ABC and 3TC daily dose
by weight bands
according to the WHO*

14-<20 kg: 300 and 150 mg
20-<25 kg: 450 and 300 mg
 \geq 25 kg: 600 and 300 mg

Methods

Twice-daily

Once-daily

Adult scored tablet



1st PK



At 0, 1, 2, 3, 4,
6, 8, 12 hr

2nd PK



Same as 1st
+ at 24 hr



DAY 0

14

28

Adverse effects including CBC, ALT, Cr were monitored during the PK study

Methods: PK analysis

Plasma concentrations measured by validated high performance liquid chromatography (HPLC)

PK parameters were calculated using WinNonlin

1. Daily area under the curve (AUC_{0-24})
2. Maximum concentration (C_{max})
3. Minimum concentration (C_{min})
4. Apparent oral clearance normalized to body weight (CL/F/kg)

**OD vs BID AUC_{0-24} and C_{max} were compared
by GMR with 90%CI**

Results

Baseline characteristics	N=30
Median age, years (IQR)	8.8 (6.6-11.3)
% Female	43
Median Body weight, kg (IQR)	21.9 (19.2-30.6)
CDC N:A:B:C, %	6:27:20:47
CD4 count, cells/mm ³ (IQR)	841 (580-1073)
CD4, % (IQR)	30 (27-35)

**No children had serious adverse events or
Abnormal laboratory results during PK study**

Abacavir PK parameters

Parameter	This study (n=30)		
	Once-daily GM (95% CI)	Twice-daily GM (95% CI)	GMR (90% CI)
AUC₀₋₂₄, mg·h/l	14.43 (12.62-16.51)	10.65 (8.63-13.14)	1.36 (1.19-1.55)
C_{max}, mg/l	5.98 (5.07-7.06)	2.11 (1.59-2.80)	2.84 (2.28-3.53)
C_{min}, mg/l	<0.025 (<0.025-0.041)	0.019 (<0.025-0.07)	NA
CL/F/kg, l/h/kg	1.26 (1.12-1.43)	1.96 (1.56-2.47)	0.65 (0.52-0.80)

Lamivudine PK parameters

Parameter	This study (n=30)		
	Once-daily GM (95% CI)	Twice-daily GM (95% CI)	GMR (90% CI)
AUC₀₋₂₄, mg·hr/l	17.70 (14.14-22.15)	18.11 (16.07-20.41)	0.98 (0.84-1.14)
C_{max}, mg/l	5.24 (3.32-5.91)	2.84 (2.25-3.06)	1.69 (1.35-2.09)
C_{min}, mg/l (median, range)	0.057 (<0.025-0.163)	0.100 (0.057- 0.284)	NA
CL/F/kg, l/h·kg	0.58 (0.47-0.71)	0.56 (0.51-0.60)	1.05 (0.87-1.25)

Discussions

ABC OD vs BID

Higher OD AUC_{0-24} than BID AUC_{0-24}

- Saturation of pre-systemic metabolism
- Similar to PENTA-13
- Lower AUC_{0-24} in 14-20 kg weight bands
 - Interaction with LPV/r

ABC PK parameters VS ARROW

Parameters of ABC	Our study (N=30)	ARROW (N=36)	
	Once-daily GM	Once-daily GM	P value
AUC ₀₋₂₄ , mg•h/l	14.43	15.28	0.45
C _{max} , mg/l	5.98	6.84	0.14
C _{min} , mg/l	<0.025	0.006	NA
CL/F/kg, l/h/kg	1.26	1.24	0.94

3TC OD vs BID

OD AUC₀₋₂₄ bioequivalent to BID AUC₀₋₂₄

- **Higher 3TC exposure in Thai children compared to historical data in adult and children**
- **No toxicity observed during PK periods**

*Chokephaibulkit K AntivirTher 2011; 16: 1287-1295.
Vanprapar N Pediatr Infect Dis J 2010; 29: 940-944.*

3TC PK parameters VS ARROW

Parameters of 3TC	Our study (N=30)	ARROW (N=36)	
	Once-daily GM	Once-daily GM	P value
AUC₀₋₂₄, mg•h/l	17.70	12.99	<0.001
C_{max}, mg/l	5.24	3.17	0.004
C_{min}, mg/l	0.057	0.050	NA
CL/F/kg, l/h/kg	0.58	0.72	0.63

Conclusions

Abacavir

- AUC_{0-24} : OD is not equivalent (higher) to BID

Lamivudine

- AUC_{0-24} : OD is bioequivalent to BID

**Support use of once-daily regimen of ABC and
3TC**



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