PENTA 15: Plasma pharmacokinetic study of once versus twice daily abacavir and lamivudine as part of combination antiretroviral therapy in HIV-1 infected children aged 3 to 36 months

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Introduction

- One challenge in treating HIV positive children is to reduce barriers to good adherence.
- Decreasing medication frequency would increase convenience of ART
- A once daily dosing regimen of ABC and 3TC has been approved for **adults**[1].
- **PENTA 13**; a PK study performed in HIV infected children aged 2 to 12 years, showed that ABC and 3TC taken once daily were well tolerated and non-inferior, in terms of PK profiles and continued RNA suppression, compared to the corresponding twice daily regimen[2].
- Only 3 children under 3 years were enrolled in PENTA 13.
- **PENTA 15** was an open-label, cross-over PK multi-centre study in children with HIV infection aged 3 to 36 months.

Objectives

- To **compare plasma PK parameters of once daily vs twice daily dosing of ABC and 3TC**
- To compare **age related differences** in the PK parameters of once vs twice daily dosing of ABC and 3TC in children in 3 age groups (3-12, 12-24 and 24-36 months)
- To describe child and family **acceptability of and adherence to** once compared to twice daily dosing

- HIV infected children
  - aged 3 to 36 months
  - HIV-1 RNA viral load either;
    - suppressed (i.e. <400 copies/ml)
    - non-suppressed, but low (i.e. 400-20 000 copies/ml)
  - Stable or rising CD4%

↓

On combination ART for at least 12 weeks, including ABC 8mg/kg twice daily and 3TC 4mg/kg twice daily (if applicable)

↓

At week 0 PK samples collected pre-dose, and at 1, 2, 3, 4, 6, 8 and 12 hours post-dose

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Children switched to ABC 16mg/kg once daily and 3TC 8mg/kg once daily (if applicable)

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At week 4 PK samples collected pre-dose, and at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose

↓

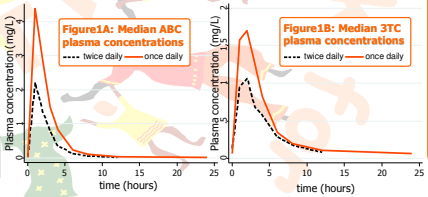
Children remained on once daily ABC and once daily 3TC (if applicable) to assess HIV RNA to week 12/24

Baseline characteristics

Table 1: Baseline characteristics

Children with two evaluable PK days	18
Age (months): 3-12 / 12-24 / 24-36	4 / 6 / 8
Sex: male	10
Route of infection: vertical	18
Ethnic origin: white / black / mixed	3 / 14 / 1
CD4%: median [IQR]	39 [35,45]
CD4 (cells/mm^3): median [IQR]	1899 [1344,3150]
HIV-1 RNA (copies/ml): <400 / ≥400	16 / 2
Number of drugs ever received: mean (SD)	3.6 (0.7)
ART combination:	
3TC,ABC,NVP (+/-ZDV or +/-D4T)	10
3TC,ABC,LPV(r) (+/-ZDV)	7
FTC,ABC,LPV(r)	1

- 18 children had two evaluable PK days; 4, 6 and 8 children in age groups 3-12, 12-24, and 24-36 months (table 1).
- All 18 children were evaluated for ABC, and 17 (94%) for 3TC.
- A GMR with a 90% CI including 1.0 and falling entirely within 0.80-1.25 was considered as bioequivalence for AUC_{0-24}.



PK results

Table 2: Primary Outcome

	N	GM twice daily (95% CI)	GM once daily (95% CI)	GMR (once vs twice)
ABC				
AUC_{0-24} (h*mg/L)	18	10.85 (8.89,13.24)	11.57 (9.89,13.53)	**1.07 (0.92,1.23)**[a]
C_{max} (mg/L)	17	2.29 (1.80,2.91)	4.68 (3.86,5.67)	2.04 (1.67,2.50) (<0.001)[b]
3TC				
AUC_{0-24} (h*mg/L)	17	9.48 (7.89,11.40)	8.66 (7.46,10.06)	**0.91 (0.79,1.06)**[a]
C_{max} (mg/L)	16	1.05 (0.88,1.26)	1.87 (1.65,2.13)	1.78 (1.47,2.16) (<0.001)[b]

[a] AUC GMR has a 90% CI. [b] C_{max} has a 95% CI and p-value for difference between once and twice daily

Table 3: Data from other paediatric and adult studies

	N	twice daily	once daily
ABC			
AUC_{0-24} (h*mg/L) GM			
PENTA 15 (95% CI)	18	10.88(8.89,13.24)	11.57 (9.89,13.53)
PENTA 13[2] (90% CI)	14	9.91(8.26,11.89)	13.37(11.80,15.16)
CAL102120[3] (95% CI)	27	7.90 (6.66,9.39)	8.52 (7.23,10.04)
C_{max} (mg/L) GM			
PENTA 15 (95% CI)	17	229 (1.80,2.91)	4.68 (3.86,5.67)
PENTA 13[2] (90% CI)	14	2.14 (1.79,2.56)	4.80 (4.04,5.71)
CAL102120[3] (95% CI)	27	1.84 (1.58,2.15)	3.85 (3.34,4.42)
3TC			
AUC_{0-24} (h*mg/L) GM			
PENTA 15 (95% CI)	17	9.48 (7.89,11.40)	8.66 (7.46,10.06)
PENTA 13[2] (90% CI)	19	8.88 (7.67,10.28)	9.80 (8.64,11.12)
EPV1001[4] (95% CI)	60	9.21 (8.81,9.63)	8.70 (8.28,9.14)
C_{max} (mg/L) GM			
PENTA 15 (95% CI)	16	1.05 (0.88,1.26)	1.87 (1.65,2.13)
PENTA 13[2] (90% CI)	19	1.11 (0.96,1.29)	2.09 (1.80,2.42)
EPV1001[4] (95% CI)	60	1.19 (1.12,1.26)	1.97 (1.84,2.11)

Paediatric studies; PENTA 15 and 13, had target total daily dose of 16mg/kg for ABC and 8mg/kg for 3TC.
Adult study; CAL102120, had target total daily dose of 8mg/kg.
Adult study; EPV1001, had target total daily dose of 4mg/kg.

Safety and efficacy

- Maintenance of virological control: at screening, 4, 8, 12 and 24 weeks 89%, 93%, 93%, 94% and 100% of children had HIV RNA <400 copies/ml, and the proportion <50 copies/ml remained stable over time.
- Maintenance of CD4 and CD4%
- No resistance seen in children with HIV-1 RNA >100 copies/ml
- 2 non-ART related SAEs (1 croup, 1 scalp laceration)
- No new CDC B and C events
- No children discontinued once daily before week 12 (1 child discontinued at week 16.3 due to fluctuating HIV RNA and adherence concerns)
- No increased toxicity

Age comparison

For **ABC**, in the oldest age group the AUC_{0-24} on twice daily was lower than for younger children (p=0.03). On once daily the middle and oldest age groups tended to have a lower AUC_{0-24} than the youngest (p=0.06). These observations are likely to be due to the small sample size per age group, and there were no linear trends with age (p=0.8 for both). There was no difference in C_{max} between age groups.
For **3TC**, on both twice and once daily dosing, there was no difference (P>0.05) among age groups for the AUC_{0-24} or C_{max}

Adherence and acceptability

- Adherence reported by carers (visual analogue scale) was 70-100%
- 71% (week 0), 80% (week 4) and 64% (week 12) reported 100% adherence.
- At week 0 one child had missed a 3TC dose the day before and another child missed a ABC, 3TC and LPV(r) dose two days before the PK dose.
- At week 4 and 12 no doses were missed in the last three days.
- At week 0, all carers thought that switching from twice to once daily would make things easier (83% a lot, 17% a little).
- After the switch, at week 12, all carers still thought the switch made things easier for them (67% a lot, 33% a little).

Conclusion

In HIV-infected children aged 3 to 36 months, the AUC_{0-24} for once daily dosing of both ABC and 3TC was bioequivalent to twice daily. As expected, C_{max} was approximately two times higher, on once compared to twice daily therapy. There was no evidence of loss of efficacy or increased toxicity on once daily therapy. Follow-up continues to week 48.
PK data from PENTA 15 which demonstrated bioequivalence of once and twice daily dosing are consistent with those from PENTA 13. However, the tendency for lower plasma concentrations of 3TC observed in younger children in PENTA 13 was not seen in PENTA 15. These results provide support for the option of once daily regimens of ABC and 3TC for children.

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