

Adherence and acceptability of once daily lamivudine and abacavir in HIV-1 infected children

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on behalf of the PENTA 13 Study Group.

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MoPe9_2C03

Background/Objectives

A very high level of adherence to ART is required for sustained viral suppression. In studies in adults, the number of pills in a regimen has been found to be a critical factor influencing adherence. Studies suggest that patients prefer compact once daily regimens, provided that efficacy and tolerability are similar to twice daily regimens.

Children with HIV face unique adherence problems as a result of the dependency of the child on their caregiver for their medication, and little research has been carried out in this area.

The objectives of this study were to assess adherence to and acceptability of **once daily** lamivudine and abacavir via questionnaires completed by caregivers of children participating in the **PENTA 13** trial.

PENTA 13 trial design

PENTA 13 was a single sequence, two-period, cross-over, open label pharmacokinetic study of twice daily (q12h) versus once daily (q24h) lamivudine (3TC) and abacavir (ABC).

HIV-1 infected children aged 2 to 12 years who had used 3TC q12h and/or ABC q12h as part of their ART regimen for at least 6 months and had a stable CD4 cell count and HIV-1 RNA viral load were recruited into the study.

24 children were enrolled between February and August 2003 from St Mary's Hospital, London, UK (n=14) and Great Ormond Street Hospital, London, UK (n=10).

Children were assessed at:

screening (week -4 to -2)
week 0: twice daily 3TC and/or ABC switched to once daily weeks 4, 12 and 24
week 48 HIV-1 RNA measurements were also available through the UK and Ireland Collaborative HIV Paediatric Study (CHIPS)

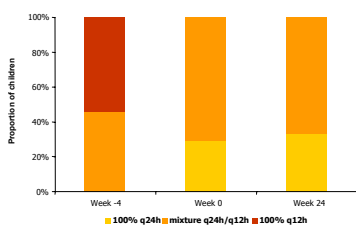
Caregivers were asked to give once daily drugs to their children in the morning up to week 4, but then they could choose the time of day to give the medicines.

Antiretroviral regimens

ART at trial entry:

- 20 children (83%) were on regimens containing 2 or 3 NRTI and 1 NNRTI
- 15 children were taking both 3TC and ABC, 8 3TC only, 1 ABC only, as part of their antiretroviral regimens.
- All NRTIs were being taken q12h except tenofovir (n=1)
- 13 children (54%) were taking all twice daily drugs in their regimens; 11 (46%) were on a mixture of once + twice daily drugs (Figure 1)

Figure 1: Proportion of children taking all once or all twice daily regimens at screening, week 0 and week 24



Note: Week 0 regimen after switching from twice daily to once daily 3TC and/or ABC

After changing 3TC and/or ABC to once daily at week 0, 17 children (71%) were on regimens containing a mixture of once + twice daily drugs; 7 (29%) were now on all once daily drugs (Figure 1).

There were very few changes in ART during the 24 weeks of follow-up. No children switched back to twice daily 3TC and/or ABC and no child switched or substituted any drug. A mixture of formulations were taken and no children changed formulations during follow-up.

Questionnaires

All caregivers were asked to complete an **adherence** questionnaire at screening, 0, 4, 12 and 24 weeks. Adherence was assessed by:

- asking about the number of doses missed over the previous 3 days.
- structured questions about difficulties taking and remembering drugs, the most difficult drugs to remember, and how much taking ART interfered with everyday life.

All caregivers were asked to complete an **acceptability** questionnaire at screening and week 24.

- Before switching to once daily, caregivers were asked how they felt or their child would benefit from switching to once daily medicines; the questions were repeated at week 24 to assess changes in views.
- Structured questions were asked about changes in the perceived ease of taking drugs, remembering to take the drugs and overall whether they preferred twice daily or once daily dosing.

Adherence

Missed doses

- ★ **Full adherence** (no missing doses in the last 3 days) was reported for 100 of the 118 (93%) completed questionnaires (n=6 children were non-adherent).
- ★ Non-adherence was generally reported as missed doses for **every** drug in the regimen (7 of 8 reports of non-adherence) with reason such as "not at home", "forgot" or "routine was different from normal".

Timing of medicines

- ★ Whereas 13 out of 23 caregivers (57%) reported timing as frequently or sometimes a problem when giving medicines at screening, this decreased to only 3 out of the 23 caregivers (13%) at week 24. This was also reflected in the fact that the number of caregivers who felt **no doses** were difficult increased after switching to once daily 3TC and/or ABC (Table 1).
- ★ 15 out of 23 caregivers (65%) thought that **morning** would be the best time to give the medicines. After changing to once daily 3TC and/or ABC, 10 out of 20 caregivers (50%) reported that their child preferred taking once daily medicines in the **morning**, 10 (50%) reported the preferred the **evening**.
- ★ Indeed, more caregivers felt their child found the **morning dose** most difficult after week 0. Conversely 6 caregivers (25%) reported the **evening dose** being most difficult for the child at week 0 which decreased to only 1 or 2 caregivers at weeks 4 to 24 after changing to once daily 3TC and/or ABC (Table 1).
- ★ Caregivers comments included: "it was easier to remember to give the medicines with breakfast" and "the child is often too tired in the evening" Others commented that evening was the best time to give the medicines because: "the morning is often too busy" and "the child may wake up late"

Table 1: Doses reported to be difficult for the child

Week	None n (%)	Morning n (%)	Evening n (%)	All n (%)
-4	13 (57%)	2 (9%)	7 (30%)	1 (4%)
0	13 (54%)	4 (17%)	6 (25%)	1 (4%)
4	16 (73%)	4 (18%)	1 (5%)	1 (5%)
12	14 (64%)	7 (32%)	1 (5%)	0 (0%)
24	16 (67%)	6 (25%)	2 (8%)	0 (0%)

Note: one missing at week -2 and 2 missing at week 12. Percentages are of non-missing values.

Adherence and viral load response

All 6 children with reported non-adherence had viral load <100 copies/ml at baseline and throughout 24 weeks of follow-up.

One child who reported a missed dose of nevirapine at week 24 subsequently rebounded (week 48 vi 27,042 copies/ml) but this was after stopping all drugs at week 24 due to adherence difficulties.

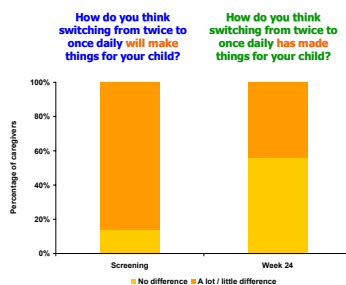
8 children had a viral load measurement >100 copies/ml either at baseline or during the 24 weeks of follow-up. None of the caregivers of these children reported missed doses in the 3 days prior to any study visit: 7 were on mixed frequency regimens after week 0 and only 1 on all once daily drugs.

Acceptability

Impact on day to day life

- At screening, 23 (96%) caregivers **thought** that switching from twice to once daily medicines **would** make things **easier** (Figure 2), with reasons such as: "will not have to worry about having to take another dose that day", "easier to remember to give medicines once a day", "allow a more flexible lifestyle (e.g. the child would be able to stay over at a friend's house)"
- 17 caregivers (71%) confirmed at week 24 that switching had made things easier. However the other 6 reported that reducing the frequency of 3TC and/or ABC had made **no difference** at all (Figure 2). Several caregivers commented that this was because "other medicines still had to be taken twice a day"

Figure 2: Impact of switching from twice to once daily



- Caregivers of all 7 children who were on a **complete once daily** regimen after switching said that switching to once daily was easier compared to only 11 of the 17 caregivers (65%) who remained on **mixed frequency** regimens (p=0.1)

Remembering to give medicines

- 20 caregivers at **screening** thought that it would be easier to remember to give medicines once daily.
- 15 agreed it was easier to remember at week 24.

Overall acceptability

21 of the 23 caregivers who answered the question said that both they and their children preferred once daily medicines. 2 caregivers said they had no preference (both were on regimens containing a mixture of twice and once daily drugs)

Summary

- Adherence to once daily 3TC and/or ABC was good.
 - 93% full adherence based on 3 day recall.
- There was no evidence of an association between non-adherence and virologic rebound.
 - but this is a small cohort of children.
 - non-adherence may not always have been reported.
- When doses were reported to have been missed, the whole medication intake was generally missed rather than the dose of one specific drug.
 - suggests missed doses were unrelated to tolerability
 - missing a once-daily dose is less forgiving than missing one dose of a twice daily regimen
- Acceptability of once daily drugs tended to be greater if the whole regimen was once daily.
- Paediatric pharmacokinetic data lag behind those of adults resulting in most drugs being utilised twice daily. Once daily medication may be even more important for children because of lifestyle restrictions and the inability to self-medicate.

Acknowledgements

We thank all the children, families and staff from the centres participating in the PENTA 13 trial.

PENTA Steering Committee: J-P Aboukir, A Babiker, S Bianche, AB Botin, P Clayden, K Butler, G Castelli-Gattisara, J Darbyshire, M Debré, M Della Negra, D Dulucicou, R de Groot, A Faye, C Gbüzürto (Chaparrero), DM Gibb, J Grosch-Wörner, M Lallemand, J Levy, H Lyall, M Marczyńska, M Mellado Peña, D Nadai, C Piccoli, JT Ramos Adellor, L Rosado, C Rizdin, H Scherpbier, M Shariand, M Stajevanovic, PA Tovo, N Valerius, AS Walker, J Wintergerst

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St Mary's Hospital, London: J Clarke, S Head, M LePrevost, H Lyall

Medical Research Council Clinical Trials Unit, London: A Babiker, L Buck, J Darbyshire, DM Gibb, H Green, L Harger, D Johnson, V Lalicicou, G Wall, AS Walker

Nijmegen University Centre for Infectious Diseases & University Medical Centre Nijmegen: K Aouat, A Bergsma, H Broekman, D Burger, C Rajmakers, C Verweij

Funding: Financial support for this trial was received from GlaxoSmithKline

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