Pharmacokinetics of Once versus Twice Daily Lamivudine and Abacavir in HIV-1 Infected Ugandan Children in the ARROW trial

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Background

Simplification of antiretroviral (ART) regimens is necessary to help maintain high adherence/acceptability and allow successful long term outcomes.

It has been shown that once daily use of Lamivudine (3TC) and Abacavir (ABC) is feasible in HIV infected European children 1 and in adults 1.

There are no data on once daily use of 3TC and ABC in children in resource-limited settings.

Objective: to compare the plasma pharmacokinetics (PK) of once versus twice daily 3TC and ABC in HIV-1 infected children in Uganda using weightbased dosing

Methods

ARROW is a randomised trial of monitoring and first-line induction-maintenance strategies in 1207 ART-naive children.

Scored tablets of Combidvir (CBV), 3TC and ABC are being used in ARROW allowing greater accuracy of division and improving dosing flexibility.

A subset of 41 children aged 3-12 years on combination ART with 3TC + ABC were enrolled to this cross-over PK study.

Total daily doses were 150-300mg, 225-450mg and 225/300-600mg for 3TC & ABC respectively in the 12-20kg, 20-25kg & >25kg weightbands respectively.

Children weighing 12-20kg took half tablets am and pm; those weighing 20-25kg took a whole tablet am and half a tablet pm, and those weighing 25-30kg took half a tablet am and pm, and a tablet of combivir am and pm.

At the end of the induction phase (twice daily dosing to week 36) of ARROW, children had PK samples collected pre-dose, 1, 2, 4, 6, 8 & 12 hrs post dose.

Children were then switched to 3TC + ABC once daily and PK sampling was repeated 4 weeks later with an additional blood draw at 24 hrs post dose.

Daily area under the curve (AUC0-24) and peak level (Cmax) were compared by geometric mean ratios (GMR)

A GMR with 90% CI falling within 0.80-1.25 was considered as bioequivalent.

Acceptability was administered at the time of switch to once daily and again 4 weeks after switch

Results

18 children were aged 3-6 years and 23 aged 7-12 years; 17 (41%) were male.

23 (56%), 14 (34%) & 4 were in the 12-20kg, 20-25kg & >25kg weightband respectively.

Exclusions: — 2 children changed weightband and dose between PK days (protocol exclusion)

— 4 children were excluded from the lamivudine analysis and 3 children were excluded from the abacavir analysis because of suspected dosing irregularities.

Table 1: Pharmacokinetic parameters of lamivudine & abacavir (*all ages combined)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3TC</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24</td>
<td>12.0</td>
<td>12.8</td>
</tr>
<tr>
<td>Cmax</td>
<td>11.1</td>
<td>12.8</td>
</tr>
<tr>
<td>GMR (once vs twice daily)</td>
<td>1.09 (0.99-1.20)</td>
<td>1.35 (1.15-1.56)</td>
</tr>
<tr>
<td>GMR (once vs twice daily, 90% CI)</td>
<td>0.96 (0.80-1.18)</td>
<td>0.96 (0.87-1.06)</td>
</tr>
</tbody>
</table>

3-6 yrs

10.2 [35%] 13.0 [53%] 1.28

12.8 [38%] 14.4 [42%] 1.16

6.6 [26%] 9.4 [51%] 1.44

1.0 [38%] 1.7 [26%] 1.75

1.8 [38%] 1.0 [38%] 1.85

3-6 yrs

5.8 [29%] 10.6 [56%] 1.83

11.5 [49%] 14.2 [68%] 1.27

3.3 [15%] 5.5 [27%] 1.67

1.7 [22%] 3.0 [33%] 1.70

1.2 [22%] 2.2 [27%] 1.80

3-6 yrs

8.7 [23%] 13.0 [77%] 1.50

11.8 [67%] 15.5 [33%] 1.31

2.2 [22%] 3.8 [40%] 1.73

1.7 [22%] 3.0 [33%] 1.70

1.2 [22%] 2.2 [27%] 1.80

Conclusions

In children aged 3-12 years, AUC0-24 of both 3TC and ABC were bioequivalent on once and twice daily regimens, whereas Cmax for once daily regimen was 76% and 64% higher for lamivudine and abacavir respectively.

Acceptability of once daily regimens in these ARROW children was very high, and preferred over twice daily.

These results suggest feasibility of once daily use of Lamivudine and Abacavir in HIV-infected children in resource-limited settings.

Children will continue to be followed on once daily dosing as part of the main ARROW trial for safety and efficacy.

Further randomised investigation of the effect of once daily dosing on virological suppression and adherence is planned.