Figure 1: Virologic suppression on twice-daily vs once-daily lamivudine+abacavir

### Absolute difference once minus twice daily (95% CI)

<table>
<thead>
<tr>
<th>Viral load (c/ml)</th>
<th>Week 0</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 c/ml</td>
<td>-4.8%</td>
<td>-1.6%</td>
<td>-2.3%</td>
</tr>
<tr>
<td>(n=666)</td>
<td>(-11.5%, +1.9%)</td>
<td>(-8.4%,+5.2%)</td>
<td>(-9.3%,+4.7%)</td>
</tr>
<tr>
<td>p</td>
<td>0.16</td>
<td>0.65</td>
<td>0.52</td>
</tr>
<tr>
<td>&lt;400 c/ml</td>
<td>-2.8%</td>
<td>-1.0%</td>
<td>-0.9%</td>
</tr>
<tr>
<td>(n=661)</td>
<td>(-8.8%,+3.2%)</td>
<td>(-7.3%,+5.3%)</td>
<td>(-7.3%,+5.5%)</td>
</tr>
<tr>
<td>p</td>
<td>0.36</td>
<td>0.76</td>
<td>0.79</td>
</tr>
<tr>
<td>&lt;1000 c/ml</td>
<td>-4.0%</td>
<td>-0.7%</td>
<td>-2.4%</td>
</tr>
<tr>
<td>(n=657)</td>
<td>(-9.7%,+1.7%)</td>
<td>(-6.8%,+5.5%)</td>
<td>(-8.6%,+3.7%)</td>
</tr>
<tr>
<td>p</td>
<td>0.17</td>
<td>0.83</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Note: excluding missing VLs at week-0 (2 twice-daily, 1 once-daily), week-48 (2 twice-daily, 6 once-daily), and week-96 (7 twice-daily, 5 once-daily) due to assay failure or died/lost before week 96.
Figure 2: <400 c/ml on twice-daily vs once-daily lamivudine+abacavir by (a) age (b) baseline VL and (c) third antiretroviral

(a) age
1-3 years 4-6 years 7+ years

(b) VL at randomisation
<80 c/ml 80-4999 c/ml 5000+ c/ml

(c) Third antiretroviral at randomisation
efavirenz nevirapine zidovudine

Note: Each panel shows VL suppression <400 c/ml in children randomised to twice-daily (black circles) vs once-daily (gray squares), according to different subgroups of age (a), VL at randomisation (b) and third drug (c). In each subgroup, VL suppression at randomisation (week 0), and 48 and 96 weeks later are connected by lines. Similar responses to once- and twice-daily lamivudine+abacavir are reflected in parallel lines. Heterogeneity (interaction) in response to once- and twice-daily lamivudine+abacavir is reflected by different relative positions of black and gray lines in the different subgroups. Overall effect of the subgroup factor is reflected by different average suppression levels in the different subgroups.
Figure 3: Predicted drug susceptibility

Note: Approximately one-half of children with genotypes were receiving triple NRTI (no NNRTI). 3TC=lamivudine, FTC=emtricitabine, ABC=abacavir, DDI=didanosine, ZDV=zidovudine, D4T=stavudine, TDF=tenofovir, EFV=efavirenz, NVP=nevirapine, ETR=etravirine, RPV=rilpivirine.
Previously untreated Ugandan/Zimbabwean HIV-infected children/adolescents aged 3 months-17 years, eligible for ART using WHO 2006 criteria

Enrolled in the ARROW Trial (n=1206)
• Randomised to initiate ART with one of three different combination regimens, all containing abacavir+lamuvudine+NNRTI
  – Arm A: abacavir+lamuvudine+NNRTI throughout
  – Arm B: abacavir+lamuvudine+zidovudine+NNRTI for 36 weeks, then abacavir+lamuvudine+NNRTI
  – Arm C: abacavir+lamuvudine+zidovudine+NNRTI for 36 weeks, then abacavir+lamuvudine+zidovudine
• Randomised using a factorial design to be managed on ART with 12 weekly CD4, haematology and biochemistry tests (Laboratory and Clinical Monitoring, LCM), or without CD4 tests and with haematology and/or biochemistry tests where clinically indicated (Clinically Driven Monitoring, CDM)

On abacavir+lamivudine-containing first-line ART for >36 weeks and expected to remain on it for >12 weeks

Eligible for the ARROW once- vs twice-daily randomisation
(see Supplementary Figure 2)
Supplementary Figure 2. CONSORT flow diagram

On lamivudine+abacavir twice daily for >36 weeks and approached for study (n=732)

Did not consent (n=63, 9%)
- reluctant to change, happy with twice daily (n=21)
- worried about forgetting dose on once-daily regimen (n=20)
- believed once-daily regimen would be less effective (n=10)
- because once-daily regimen would increase pill burden (n=5)
- other (n=7)

Randomised (n=669)

Allocated to twice-daily (n=333)
- Analysed (n=333)
  - Stayed on twice-daily initially (n=333)
    - Ever moved off twice-daily dosing (n=11)
      - switched to second-line (n=6)
      - carer requested once-daily (n=2)
      - prescription error (n=1)
      - unknown (n=2)
    - Not known to have died, last seen before 16 Mar 2012 (study end) (n=3)
    - Died before 16 Mar 2012 (n=4)
    - Median (IQR) follow-up: 2.2 years (2.0-2.4)

Allocated to once-daily (n=336)
- Analysed (n=336)
  - Moved to once-daily (n=336)
    - two moved late, 2 and 11 weeks after randomisation respectively
    - Ever moved off once-daily dosing (n=18)
      - switched to second-line (n=7)
      - carer requested twice-daily (n=5)
      - prescription error (n=1)
      - unknown (n=1)
      - carer error (n=4)
    - Not known to have died, last seen before 16 Mar 2012 (study end) (n=4)
    - Died before 16 Mar 2012 (n=1)
    - Median (IQR) follow-up: 2.2 years (2.0-2.4)
Supplementary Figure 3: IAS NRTI mutations

Note: Approximately one-half of children with genotypes were receiving triple NRTI (no NNRTI).
p>0.05 comparing twice- vs once-daily.
Randomisation occurred after at least 36 weeks on first-line ART.
Supplementary Figure 4: Self-reported missing any ART pills in the last 4 weeks

(a) All children: global p=0.93

(b) Lamivudine+abacavir+nevirapine: global p=0.59

(c) Lamivudine+abacavir+efavirenz: global p=0.62

(d) Lamivudine+abacavir+zidovudine: global p=0.23