**KONCERT**

A Kaletra ONCE daily Randomised Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children (PENTA 18).

**ISRCTN02452400**
**EUDRACT: 2009-013648-35**

**Protocol, version 1.7**

Protocol date 23rd April 2013

**Authorised by:**
Name: Carlo Giaquinto  
Role: Chair of PENTA Steering Committee

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Date: 23rd April 2013
GENERAL INFORMATION

This document describes KONCERT; a trial conducted by the Paediatric European Network for Treatment of AIDS (PENTA) and provides information about procedures for enrolling children. The protocol should not be used as an aide-memoire or guide for the treatment of other children; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering children for the first time are advised to contact one of the co-ordinating Trials Units to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Trials Unit, who will transfer these to the appropriate medical expert.

The trial will be jointly co-ordinated and monitored by the MRC Clinical Trials Unit, UK, INSERM SC10-US019, France, and Program for HIV Prevention and Treatment (PHPT), Thailand. Liaison between the Trials Units and clinical centres in each country will be similar to that organised for other PENTA trials, with a combination of direct liaison and liaison via a local co-ordinating centre. The trial will be supervised by the KONCERT Trial Management Group (TMG) who will report to the PENTA Steering Committee (see Appendix 12 for the committee structure within PENTA). The PENTA Steering Committee may decide to terminate the trial for any reason including the recommendation of the PENTA Independent Data Monitoring Committee (IDMC).

- Compliance
  The trial will be conducted in compliance with the protocol, EU Clinical Trials Directive 2001/20/EC Article 2, GCP directive 2005/28/EC and national data protection legislation.

- Sponsor
  Paediatric European Network for Treatment of AIDS (PENTA) Foundation.

Medical Research Council is co-sponsor for UK sites.

- Funder
  Paediatric European Network for Treatment of AIDS (PENTA) - funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694 with financial support for this trial from Abbott Laboratories

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<td>AUC</td>
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<td>BID</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
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<td>UK &amp; Ireland Collaborative HIV Paediatric Study</td>
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<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
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1 SUMMARY

1.1 Aims and Objectives
The trial will evaluate the pharmacokinetics, safety, efficacy and acceptability of twice- and once-daily dosing of lopinavir/ritonavir tablets (Kaletra) dosed by weight in HIV-1 infected children who are currently taking lopinavir/ritonavir as part of their combination antiretroviral therapy and who are currently achieving virological suppression (<50 copies/ml). Specifically:

- To confirm weight-based dosing recommendations by evaluating the pharmacokinetics of twice-daily lopinavir/ritonavir half strength formulation tablets dosed on body weight and comparing to historical adult and paediatric data of pharmacokinetics of lopinavir/ritonavir soft gel capsules and oral solution respectively (1, 2).
- To compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children.
- To evaluate whether once-daily dosing of lopinavir/ritonavir is comparable to twice-daily dosing in terms of virological suppression at 48 weeks. Adherence and acceptability will also be compared.

1.2 Design
KONCERT is a prospective, open label, multicentre, randomised (1:1) phase II/III trial. Children will be randomised (1:1) either to continue the same HAART regimen with lopinavir/ritonavir tablets taken twice-daily or to continue the current HAART regimen but switch to lopinavir/ritonavir tablets dosed once-daily. Randomisation will be stratified by body weight band (≥15 to ≤25kg, >25 to ≤35kg, >35kg). Children will be followed for a minimum 48 weeks.

Once-daily dosing of lopinavir/ritonavir will be the same total daily dose as twice-daily dosing but lopinavir/ritonavir will only have to be taken at one time during the day.

A pharmacokinetic (PK) study will be performed on a minimum of the first 16 children enrolled in each of the three body weight bands; a minimum total of 48 children. Children enrolled in the PK study will have lopinavir and ritonavir pharmacokinetics determined on twice-daily dosing before randomisation. Only if randomised to once-daily dosing, children will have a second pharmacokinetic assessment of lopinavir and ritonavir at 4 weeks. If a child in the PK study does not have full evaluable PK data, further children will be recruited to the PK part of the trial from the relevant body weight band as replacements. Children with non-evaluable PK data will still continue to be followed in their randomised arm.

The non-inferiority design of the randomised part of the trial requires 160 children to be enrolled (80 in each arm) in order to exclude differences of 12% in the percentage of children maintaining HIV-1 RNA <50 copies/ml to 48 weeks between once-daily and twice-daily dosing, with 80% power and 5% significance level (one-sided).

For an overview of the trial design please see schematic diagram in section 1.7.

1.3 Population
160 HIV-1 infected children aged <18 years, ≥15kg in weight and able to swallow tablets, with viral suppression (HIV-1 RNA <50 copies/ml) for at least the prior 24 weeks. Participants must have been on an antiretroviral regimen that includes lopinavir/ritonavir for at least 24 weeks.

At the screening visit lopinavir/ritonavir should be changed to tablet formulation if the child is not already taking tablets and the current dose of lopinavir/ritonavir (twice-daily) should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary. The
children enrolled in the PK study should change to 100/25mg strength lopinavir/ritonavir tablets only.

Children will be recruited from clinical centres in countries participating in the PENTA, HIV NAT (Thailand) and PHPT (Thailand) networks.

1.4 Outcome measures

Primary Outcomes:
- HIV-1 RNA ≥50 copies/ml (confirmed) at any of week 4, 8, 12, 24, 36 or 48
- AUC, C_{min} and C_{max} values of lopinavir after twice-daily dosing compared to historical adult (1) and paediatric (2) data
- AUC, C_{min} and C_{max} values of lopinavir after once-daily and twice-daily dosing (in the same children)

Secondary Outcomes:
- HIV-1 RNA <400/<50 copies/ml at 24 and 48 weeks
- HIV-1 RNA ≥400 copies/ml at any of week 4, 8, 12, 24, 36 or 48
- number of HIV-1 mutations present at week 4, 8, 12, 24, 36 or 48 conferring resistance to drugs taken at randomisation or during the trial
- change in CD4 (absolute and percentage) from baseline to 24 and 48 weeks
- change in ART (defined as any change from the ART regimen at randomisation)
- ART-related grade 3 or 4 clinical and laboratory adverse events
- new CDC stage C diagnosis or death
- child and family acceptability of and adherence to twice-daily lopinavir/ritonavir 100/25mg tablets dosed on body weight, over 48 weeks as assessed by patient/carer completed questionnaires
- child and family acceptability of and adherence to once-daily compared to twice-daily dosing of lopinavir/ritonavir tablets, over 48 weeks as assessed by patient/carer completed questionnaires

Tertiary Outcomes:
- Tanner Scale at 24 and 48 weeks

1.5 Follow-up

All children will be seen for clinic visits at weeks -4 to -2 (screening), 0, 4, 8, 12, 24, 36 and 48. Where required, PK assessments will be carried out at weeks 0 and 4.

The paediatrician may request more frequent visits for children if required. The flowsheet (section 1.8) indicates the minimum for protocol completion and data recording. However, it is the investigator’s responsibility to see participants as frequently as necessary, particularly for the monitoring of adverse events.

All children with a viral load ≥50 copies/ml will be asked to come back as soon as possible and within 4 weeks for a confirmatory re-test.

1.6 Duration

Children will be recruited over 24 months and followed for a minimum of 48 weeks. The end of study visits will coincide with the completion of 48 weeks’ follow-up for the last patient enrolled. Participants being followed after week 48 should be seen every 12 weeks, until the last child has completed follow-up. Participants randomised to the once-daily dosing arm should continue to take
once-daily lopinavir/ritonavir unless the clinician or the family have concerns which they should discuss with the relevant Trials Unit.

1.7 Schematic diagram

**Screening visit**
A minimum of 48 children (at least 16 per weight band, all on 100/25mg strength lopinavir/ritonavir tablets) allocated to PK group
All children, on tablet formulation and dosed according to FDA body weight bands, undergo clinic visit

**160 eligible children aged <18 years, ≥15kg, taking lopinavir/ritonavir, BID**

**Week 0**
A minimum of 48 children undergo full PK
Remaining children undergo clinic visit

**Children randomised (1:1) to QD or BID lopinavir/ritonavir**

**Week 4**
80 children on QD lopinavir/ritonavir
A minimum of 24 children undergo full PK (all on 100/25mg strength lopinavir/ritonavir tablets) Remaining children undergo clinic visit

**Week 4**
80 children on BID lopinavir/ritonavir
No further full PK
All 80 children undergo clinic visit

**Follow-up**
Clinic visits - weeks 0, 12, 24, 36, 48 and every 12 weeks until last patient reaches 48 weeks
If VL ≥ 50 repeat HIV-1 RNA viral load test within 4 weeks.

NB: 48 children is the minimum number of children who will be recruited to the PK study. If a child in the PK study does not complete one or both PK assessments (if randomised to switch to lopinavir/ritonavir tablets dosed once-daily) or has no evaluable PK data, further children will be recruited to the PK part of the trial from the relevant body weight band as replacements. Children with non-evaluable PK data will still continue to be followed in their randomised arm.
## 1.8 Assessment flowsheet

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>SCREENING -4 TO -2</th>
<th>0 (FASTING)</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24 (FASTING)</th>
<th>36</th>
<th>48 (FASTING)</th>
<th>Further follow-up</th>
<th>END OF TRIAL VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed informed consent</td>
<td>X</td>
<td>(CONFIRM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment a</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Local HIV-1 RNA viral load</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
<td>X</td>
<td></td>
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<tr>
<td>T cell lymphocyte subsets</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
<td>X</td>
<td></td>
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<tr>
<td>Biochemistry b</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
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<td>Haematology c</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
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<td></td>
</tr>
<tr>
<td>Lipids and glucose (fasting) d</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 48 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test e</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 24 weeks</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tanner scales f</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 24 weeks</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 12 weeks</td>
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<td>Adherence questionnaire</td>
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<td>X</td>
<td>X</td>
<td>Every 24 weeks</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Acceptability Questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
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<td>Full PK assessment</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Note: If insufficient blood is drawn, priorities are: T cell subsets, local HIV-1 RNA, plasma store, lipids/glucose, biochemistry, haematology.  

(a) Clinical assessment: Height & weight (adjust doses); Presence of adverse events and change in HIV disease stage (including clinical lipodystrophy) not measured at screening visit.  
(b) Biochemistry: Creatinine, Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin.  
(c) Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets.  
(d) Lipids/Glucose: Triglycerides, Cholesterol (Total, HDL, LDL, VLDL), Glucose.  
(e) Pregnancy Test: This pregnancy test could be either a urine sample or blood sample test. This test will be performed for all females of childbearing potential at different time-points during the trial or if requested. The initial pregnancy test must be done within 72 hours of enrolment and its results must be received before randomisation.  
(f) Tanner scales: Only in children >30kg or 9 years old.  
(g) 8ml in EDTA for separation and storage of plasma at -80°C (see Manual of Operations for instructions for plasma handling and storage). Only 6ml if child having a full PK assessment on that visit.  
(h) Acceptability questionnaire: Only children on OD arm if switch back to BID dosing. Complete one questionnaire at the time of switching.  
(i) All children enrolled in PK study – assessment on BID lopinavir/ritonavir.  
(j) Children in PK study randomised to OD dosing of lopinavir/ritonavir.
2 BACKGROUND

2.1 Introduction

Several issues complicate treatment of HIV-1 infection in children and adolescents. One challenge is to give the correct antiretroviral dose to provide adequate drug exposure as a child grows to minimize toxicity and maintain efficacy. Dosing guidelines typically use weight or body surface area to adjust doses for children. As drug pharmacokinetics in children differ greatly from that in adults due to age-related variations in renal, hepatic and gastric function, which result in altered drug absorption and metabolism, it is important to conduct studies in children to inform dosing guidelines rather than extrapolate from adult data.

The protease inhibitor (PI) lopinavir/ritonavir (Kaletra) is recommended by European and American guidelines for treatment of children with HIV-1 infection and has been approved for use in children by the European Medicines Agency (EMEA) (age 2 years and older) and the United States Food and Drug Administration (FDA) (age 14 days and older). Lopinavir/ritonavir is available as oral solution or tablets in dosage strengths of 200/50 mg and 100/25 mg. The 200/50 mg tablet replaced the original soft-gel capsule in 2006, and the half-strength lopinavir/ritonavir tablet (100/25 mg) was approved by the EMEA and FDA in 2008, designed to provide flexible dosing for paediatric patients. Lopinavir/ritonavir tablets are approved for paediatric use, to be taken twice-daily. The number of tablets to be taken as the child grows is based on body weight bands under FDA approval whereas it is based on body surface area (BSA) by the EMEA. This leads to some differences in the number of tablets recommended for a child (see section 2.2.1), e.g. a child who weighs 40kg, which is approximately equivalent to a BSA of 1.3m$^2$, would be recommended to take three 100/25mg tablets twice-daily under the EMEA approval compared to four 100/25mg tablets twice-daily under FDA approval. No studies have been conducted to evaluate these dosing guidelines in children taking the half strength paediatric tablets.

Another challenge for the treatment of HIV-1 infection in children and adolescents is to improve medication adherence in particular for children who rely on caregivers for medication administration, and for adolescents undergoing the transition to adulthood. Adherence is related to several factors, including palatability and number of pills or volume of medication, complexity of medication schedules and interference with the child or caregiver’s daily activities. Decreasing the frequency of dosing is likely to increase convenience and enhance adherence to antiretroviral therapy in HIV-1 infected children and adolescents.

Six nucleoside reverse transcriptase inhibitors (NRTIs) are currently available for the treatment of HIV-1 infection in children, five in twice-daily dosing schedules and one, emtricitabine (FTC), is the only NRTI currently approved for use as a once-daily component of combination therapy for children in Europe. The use of lamivudine (3TC) and abacavir (ABC) once-daily has been studied in children (3) but is not yet approved. The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) is also approved for use in once-daily dosing schedules for children, as is the protease inhibitor atazanavir for children over 6 years. All of the other 7 protease inhibitors available for children have to be taken twice or three times a day. Therefore, the number of once-daily only treatment options for paediatric patients is limited.

Randomised trials in antiretroviral-naive adults have shown that lopinavir/ritonavir taken once-daily has similar efficacy to twice-daily dosing (4-7) and is approved by the FDA for antiretroviral-naive adults. Furthermore, a recent randomised trial in antiretroviral-experienced adults showed similar results and increased adherence in the OD dosing arm compared to the BID arm (8). A small pharmacokinetic study of OD dosing in children showed encouraging results (9). The availability of additional agents with a once-daily dosing schedule would allow paediatricians to construct compact treatment regimens which are tailored to patient needs.
2.2 Lopinavir/ritonavir approved dosing in paediatric subjects

The approved EMEA paediatric dose for lopinavir/ritonavir is 230/57.5 mg/m\(^2\) given twice-daily (300/75 mg/m\(^2\) given twice-daily if given with nevirapine, efavirenz, (fos)amprenavir or nelfinavir) for children aged 2 years and older, for comparable exposure to that observed in adults. The approved FDA dose is the same except the recommended dose for children aged 14 days to 6 months is 300/75 mg/m\(^2\) given twice-daily regardless of other antiretrovirals given. The licensing trial in children >6 months of age for lopinavir/ritonavir was a two-dose study of lopinavir/ritonavir with or without nevirapine in NNRTI-naive subjects. A greater proportion of subjects had viral load suppression in the higher dose group (HIV-1 RNA <400 copies/ml at week 12 was 63% [17 out of 27] for subjects taking 230/57.5 mg/m\(^2\) twice-daily compared to 72% (21 out of 29) for subjects taking 300/75 mg/m\(^2\) twice-daily) but this difference was not statistically significant (p=0.6) [1]. In clinical practice, some paediatricians, therefore, recommend the higher dose regardless of concomitant therapy, especially for heavily pre-treated children where reduced susceptibility to lopinavir is suspected.

The UK/Irish paediatric cohort (CHIPS) has followed 1322 HIV-infected children since January 2000. To the end of December 2007 there were 333 children who have ever taken lopinavir/ritonavir. Of the 2748 lopinavir doses recorded during quarterly visits, 6% were at least 10% below the lower 460mg/m\(^2\) daily target (<410 mg/m\(^2\)), 9% were at least 10% above the higher 600mg/m\(^2\) target (>660 mg/m\(^2\)), with most doses between 410 and 530mg/m\(^2\) (46%) or between 530 and 660mg/m\(^2\) (39%). In multivariate analysis, older children, children of higher weight-for-age and height-for-age, those without prior AIDS or those with lower viral loads were more likely to receive lower doses, as well as those on once-daily dosing. However, there was no clear evidence that higher doses were associated with improved VL suppression (10).

The number of paediatric tablets to be taken as the child grows to meet the above target doses are based on body weight bands under FDA approval compared to BSA under EMEA approval (see section 2.2.1). No studies have been conducted to evaluate dosing guidelines in children taking the paediatric tablets. Dosing on body surface area usually gives a better prediction of adequate AUCs than dosing on body weight, because hepatic metabolism is more strongly related to BSA than to body weight (11). This is mainly true for very young children and less important for older children when dosing on body weight gives similar pharmacokinetics to BSA. Dosing by body weight bands is also easier for paediatricians.

2.2.1 EMEA and FDA approved doses for lopinavir/ritonavir (not given with NNRTI, fosamprenavir or nelfinavir)

**EMEA** (aged 2 years and older)

<table>
<thead>
<tr>
<th>Body Surface Area (m(^2))</th>
<th>Approx equivalence weight (kg)</th>
<th>Number of 100/25mg tablets twice-daily</th>
<th>Exposure twice-daily (BSA) (mg/m(^2))</th>
<th>Exposure twice-daily(weight) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5 to &lt;0.9</td>
<td>≥10 to &lt;24</td>
<td>2</td>
<td>400 to 222</td>
<td>20 to 8</td>
</tr>
<tr>
<td>≥0.9 to &lt;1.4</td>
<td>≥24 to &lt;44</td>
<td>3</td>
<td>333 to 214</td>
<td>12.5 to 7</td>
</tr>
<tr>
<td>≥1.4</td>
<td>≥44</td>
<td>4</td>
<td>&lt;286</td>
<td>&lt;9</td>
</tr>
</tbody>
</table>

**FDA** (aged 6 months and older)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Approx equivalence BSA (m(^2))</th>
<th>Number of 100/25mg tablets twice-daily</th>
<th>Exposure twice-daily (BSA) (mg/m(^2))</th>
<th>Exposure twice-daily(weight) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 to ≤25</td>
<td>≥0.65 to ≤0.92</td>
<td>2</td>
<td>308 to 217</td>
<td>13 to 8</td>
</tr>
<tr>
<td>&gt;25 to ≤35</td>
<td>&gt;0.92 to ≤1.2</td>
<td>3</td>
<td>326 to 250</td>
<td>12 to 9</td>
</tr>
<tr>
<td>&gt;35</td>
<td>&gt;1.2</td>
<td>4</td>
<td>&lt;333</td>
<td>&lt;11</td>
</tr>
</tbody>
</table>
2.3 Pharmacokinetics of lopinavir/ritonavir in paediatric subjects
The lopinavir mean (SD) steady state AUC$_{0-12h}$, C$_{max}$ and C$_{min}$ in 12 HIV-infected children after intake of 230/57.5 mg/m$^2$ lopinavir/ritonavir oral solution without nevirapine twice-daily were 72.6 (31.1) mg/L.h, 8.2 (2.9) mg/L, and 3.4 (2.1) mg/L, respectively, which were similar plasma concentrations to adult subjects receiving the normal dose of 400/100mg twice-daily without nevirapine. The absolute bioavailability of lopinavir has not been determined. Lopinavir/ritonavir tablets may be taken with or without food and have shown less pharmacokinetic variability under all meal conditions compared to lopinavir/ritonavir soft capsules. Lopinavir is 98-99% bound to plasma proteins. The drug is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by CYP3A. The half-life of lopinavir in the presence of ritonavir is 5-6h, with an apparent oral clearance of 6-7 L/h.

2.4 Side effects/adverse reactions of lopinavir/ritonavir in paediatric subjects
Adverse events that can be expected from the use of lopinavir/ritonavir in children are: diarrhoea, abdominal pain, asthenia, headache, nausea, vomiting, insomnia and rash. Laboratory abnormalities include hyperbilirubinemia, hepatic enzyme elevations, hyperlipidemia. Cases of pancreatitis have also been reported.

Lopinavir/ritonavir prolongs the PR and QT intervals on the electrocardiogram in some patients and should be used with caution in patients who have preexisting structural heart disease, conduction system abnormalities, or other cardiac diseases.

2.5 Once-daily dosing of lopinavir/ritonavir - adults
Two randomised controlled trials in antiretroviral-naive HIV-1 infected adults suggested that lopinavir 800/200mg soft-gel capsules taken once-daily had similar virologic efficacy, immunological improvement and rates of resistance to lopinavir 400/100mg dosed twice-daily [4-6]. Although both trials observed statistically significantly lower minimum concentrations of lopinavir during once-daily dosing compared to twice-daily dosing, there was no apparent association with reduced virologic response. The larger trial randomised 190 ART-naïve subjects to either twice-daily lopinavir/ritonavir soft-gel capsules with tenofovir (TDF) and FTC once-daily (n=75) or to a complete once-daily regimen of lopinavir/ritonavir, TDF and FTC (n=115). The lopinavir mean (SD) steady state AUC$_{0-24h}$, C$_{max}$ and C$_{min}$ in 24 ART-naive adults after 4 weeks of once-daily dosing were 154.1 (61.4) mg/L.h, 11.8 (3.7) mg/L and 1.7 (1.6) mg/L, compared to 181.8 (85.0) mg/L.h, 9.7 (4.1) mg/L, and 5.0 (2.9) mg/L in 13 subjects in the twice-daily group. In all subjects, after 48 and 96 weeks of treatment, 70% and 57% in the once-daily group had HIV-1 RNA levels less than 50 copies/ml compared to 64% and 53% in the twice-daily group, respectively [5-6]. A recent trial comparing lopinavir/ritonavir tablet formulation once-daily (n=333) versus twice-daily (n=331) in ART-naive adult subjects showed similar results at 48 weeks with 77% versus 76% of the subjects achieving HIV-1 RNA levels less than 50 copies/ml respectively [7].

A trial of 72 antiretroviral-experienced adults suppressed on their first PI-containing regimen randomised to once-daily lopinavir/ritonavir, TDF and 3TC or continued on their existing regimen found no statistically significant difference in the maintenance of virologic suppression between the two groups, with 44 of 50 (88%) subjects in the once-daily group suppressed <50 copies/ml at week 48 compared to 21 of 22 subjects (95.5%) in the twice-daily group. Lower C$_{min}$ concentrations observed in the once-daily dosing arm did not appear to predispose patients to virologic failure [12].
2.6 Once-daily dosing of lopinavir/ritonavir - paediatric subjects

There have been several pharmacokinetic studies of once-daily dosing of lopinavir/ritonavir in children. Rosso, et al (13) found that in ART-naïve children, $C_{\text{min}}$ concentrations were significantly lower in 7 children who switched to lopinavir/ritonavir once-daily dosing after a month of twice-daily dosing (oral solution or soft-gel capsule) compared to 21 children on lopinavir/ritonavir dosed twice-daily; median (IQR) $C_{\text{min}}$ of 1.6 (0.8 to 6.9) mg/L compared to 7.9 (5.5 to 9.8) mg/L respectively. However inter-patient variability was high and there was no difference in $C_{\text{max}}$. Van der Lee et al (14) found in 19 treatment-experienced children stable on highly active ART (HAART) and taking lopinavir/ritonavir oral solution and/or capsules, that 460/115 mg/m$^2$ once-daily led to mean pharmacokinetic parameters comparable to data of 800/200 mg once-daily in adults, however there was also higher variability observed in the trough levels in children; AUC$_{0-24h}$, $C_{\text{max}}$ and $C_{\text{min}}$ were 149.8 (58.8) mg/L/h, 10.8 (2.9) mg/L and 2.9 (3.7) mg/L respectively. In a subsequent study where 15 children on a stable once-daily regimen containing lopinavir/ritonavir capsules switched to lopinavir/ritonavir tablets (200/50mg), overall exposure to lopinavir and ritonavir appeared to be higher than previously found for capsules and between patient variability was lower; AUC$_{0-24h}$, $C_{\text{max}}$ and $C_{\text{min}}$ were 217.9 (44.9) mg/L/h, 14.8 (2.4) mg/L and 3.1 (2.6) mg/L respectively. All children had undetectable viral loads (<50 copies/ml) during 24 weeks of follow-up (9). However, there have been no randomised studies looking at the efficacy of once-daily dosing of lopinavir/ritonavir in children.

2.7 Rationale and objectives

Evaluating the current dosing guidelines in children taking the half-strength paediatric tablets will provide reassurance that the recommended lopinavir/ritonavir dose provides adequate drug exposure and maintains efficacy. As dosing by body weight gives similar pharmacokinetics to dosing by body surface area in older children (who are also the children able to swallow tablets) and dosing by body weight bands is also easier for paediatricians to calculate, an objective of this trial will be to confirm the FDA weight band-based recommendations of twice-daily lopinavir/ritonavir 100/25mg tablets in children who are currently taking lopinavir/ritonavir as part of their combination antiretroviral therapy and achieving virological suppression. The pharmacokinetics of twice-daily lopinavir/ritonavir half-strength formulation tablets dosed on body weight band will be evaluated and compared to historical adult (1) and paediatric (2) data.

Decreasing the frequency with which medication needs to be taken in a day is likely to increase convenience and to enhance adherence to antiretroviral therapy in HIV-1 infected children. Furthermore, for agents that need to be taken with food, parents have more flexibility in selecting the most appropriate time point during the day when a child takes medication. The possibility of complete once-daily regimens for children and adolescents is attractive.

In ART-naïve adults, AUCs of twice-daily and once-daily dosing are equivalent for lopinavir/ritonavir resulting in antiviral efficacy and licensed once-daily dosing by the FDA. The limited data in ART-experienced adults also suggest that once-daily lopinavir/ritonavir is comparable to twice-daily dosing. Pharmacokinetic studies have shown similar exposure of lopinavir dosed once-daily in paediatric subjects to adults, and therefore the rationale is that the AUCs of twice-daily and one-daily dosing in children will provide similar results, which in turn will show equivalent antiviral efficacy. The lower $C_{\text{min}}$ concentrations observed on once-daily dosing of lopinavir/ritonavir soft-gel capsules and/or oral solution in adults and children appear not to be associated with reduced virological response and higher exposure, and less variability has been observed in children taking the tablet formulation of lopinavir.

Therefore the pharmacokinetic profile and efficacy of once-daily lopinavir/ritonavir tablets as part of combination ART therapy should be further explored in a comparative trial versus twice-daily dosing of lopinavir/ritonavir in children. This trial will evaluate whether once-daily dosing of lopinavir/ritonavir is comparable to twice-daily dosing in terms of virological suppression over 48
weeks, and to compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children.

2.8 Risks and benefits
As this trial is a treatment strategy study, there are no additional drug toxicity risks to participants beyond those associated with their routine HAART. The main risk associated with undertaking this trial is that the strategy of taking lopinavir/ritonavir once-daily will prove less effective in maintaining viral suppression and that viral evolution with the emergence of resistance might occur. There is the small potential risk that such resistance might render a drug or class of drugs ineffective which could in turn limit future therapeutic options. However, lopinavir/ritonavir is known to have a very high genetic barrier to resistance and therefore the emergence of resistance is unlikely. Taking the entire daily amount of lopinavir/ritonavir in a single dose, may cause undesirable side effects such as diarrhoea. Although this should improve after a few days, patients and families are encouraged to raise their concerns to their paediatricians and nurses.

The potential benefits are that this strategy would afford an improvement in quality of life for children, resulting in improved long-term adherence, counteracting the trend toward decline in adherence over time and thus better maintaining regimen efficacy. It will also give important information on the pharmacokinetics of both once- and twice-daily dosing of half-strength lopinavir/ritonavir, which will provide more flexible dosing for paediatric patients and inform future treatment guidelines.

3 SELECTION OF CENTRES/CLINICIANS

3.1 Clinical Sites
Sites invited to enrol children in KONCERT will usually have previously collaborated in PENTA trials with the MRC Clinical Trials Unit (CTU), INSERM, or PHPT. In the case of a new site wishing to participate, the site will need to demonstrate sufficient resources to conduct clinical trial research with children. MRC CTU, INSERM or PHPT staff will visit new sites prior to the trial commencing at that site in order to carry out a site set-up visit. This visit should be attended by the principal investigator at that site (the paediatrician), the clinic nurse(s), representatives from the laboratory and pharmacy, and any other staff who will be involved in KONCERT. At the trial set-up visit the trial management staff should ensure that the following minimum criteria are met before the site enrols patients into the trial:

- The paediatrician should be experienced in the management of children with HIV or work in close contact with a specialist HIV unit/site.
- Staff involved in the trial should have training in Good Clinical Practice (GCP)
- Bloods for PK days and plasma storage will be handled in well-organised laboratories with sufficient storage space and a good record system (or can be sent to a centralised laboratory)
- Pharmacy staff are able to keep detailed records of the trial medications prescribed
- Good communication between all of the above departments
- Where sites are participating in the pharmacokinetic study, there are sufficient support staff (e.g. research nurses) and facilities to carry out the PK days

Training will be provided for all sites participating in KONCERT. The principal investigator will sign an Investigator’s Agreement for that institution on behalf of all staff at that site who will be working on KONCERT. The principal investigator will sign to ensure:
• The institution has an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
• All staff assisting with the trial is adequately informed about the protocol, the investigational products and their trial related duties.
• The trial will be conducted in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights or welfare of patients.
• The trial will be conducted in compliance with GCP and applicable regulatory requirements.
• The institution will permit monitoring and auditing by the relevant Trials Unit and inspection by the appropriate regulatory authorities. Direct access will be made available to all trial related sites, data/documents and reports.
• The institution will maintain a trial master file (TMF), which will contain essential documents for the conduct of the trial.
• All trial data will be submitted in a timely manner and as described in the protocol.
• All Serious Adverse Events (SAEs) will be reported immediately to the relevant Trials Unit (within one working day of the investigator becoming aware of the event). The initial SAE report shall be promptly followed by detailed written reports.
• No data on trial patients will be disclosed without the approval of the Trial Steering Committee (TSC).
• All trial related documents will be retained for at least 15 years after the completion of the trial.

In addition and in compliance with ICH GCP all institutions participating in the trial will complete a delegation log and forward this to the relevant Trials Unit. Each person working on KONCERT must complete a section of this log and indicate their responsibilities. The Trials Unit must be immediately notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the TMF at the institution and also at the Trials Unit.

3.2 Site management
Sites in the United Kingdom and Ireland are managed by the MRC CTU. Sites in the Netherlands, Germany, Italy, Brazil, and Thailand (HIV-NAT) are managed by the MRC CTU in collaboration with national co-ordinators. Sites in France are managed by INSERM SC10-US019. Sites in Spain, Portugal, Romania and Argentina are managed by INSERM SC10-US019 in collaboration with national co-ordinators. PHPT sites in Thailand are managed directly by PHPT.

4 DESIGN

4.1 Design of Trial
KONCERT is a prospective, open label, multicentre, randomised (1:1) phase II/III trial. Children will be randomised 1:1 into two groups:
1. Twice-daily lopinavir/ritonavir (BID arm)
2. Once-daily lopinavir/ritonavir (OD arm)

Randomisation will be stratified by body weight band (≥15 to ≤25kg, >25 to ≤35kg, >35kg).

It is planned to recruit 160 young people over 18 months. All participants must be followed until the last participant has completed 48 weeks of follow-up.
4.2 Trial Interventions
Children will be randomised (1:1) either to continue the same HAART regimen with lopinavir/ritonavir tablets taken twice-daily or to continue the current HAART regimen but switch to lopinavir/ritonavir tablets dosed once-daily.

Once-daily dosing of lopinavir/ritonavir will be the same total daily dose as twice-daily dosing but lopinavir/ritonavir will only have to be taken at one time during the day rather than two.

At the screening visit lopinavir/ritonavir should be changed to tablet formulation if the child is not already taking tablets and the current dose of lopinavir/ritonavir (twice-daily) should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary. A minimum of 48 children enrolled in the PK study should change to 100/25mg strength lopinavir/ritonavir tablets only (see below).

4.3 PK study
A pharmacokinetic study will be performed on a minimum of the first 16 children enrolled in each of the three body weight bands; a minimum total of 48 children. These children must be willing to change to taking half-strength formulation lopinavir/ritonavir tablets (100/25mg) only, dosed according to the FDA recommended dosing plan based on their body weight, at the screening visit.

Children enrolled in the PK study will have lopinavir and ritonavir pharmacokinetics determined on twice-daily dosing at week 0. The PK assessment should be underway before the arm, the child is randomised to, is revealed. If randomised to once-daily dosing, children will have a second pharmacokinetic assessment of lopinavir and ritonavir at 4 weeks. If a child in the PK study does not have full evaluable PK data, further children will be recruited to the PK part of the trial from the relevant body weight band as replacements. Children with non-evaluable PK data will still continue to be followed in their randomised arm.

Once it has been confirmed that evaluable PK data have been obtained for each weight band on twice- and once-daily dosing, it will no longer be necessary for children entering the trial to be willing to take half strength formulation lopinavir/ritonavir tablets only (although all children must still fulfil all eligibility criteria listed in section 5.1 and 5.2); subsequent children enrolled will not undergo full PK analysis during the trial.

All samples for the PK study will be analysed in the protocol pharmacology laboratory in Nijmegen, the Netherlands.

4.4 Outcome measures
**Primary Outcomes:**
- HIV.1 RNA ≥50 copies/ml (confirmed) at any of week 4, 8, 12, 24, 36 or 48
- AUC, C_min and C_max values of lopinavir after twice-daily dosing compared to historical adult [1] and paediatric [2] data
- AUC, C_min and C_max values of lopinavir after once-daily and twice-daily dosing (in the same children)

**Secondary Outcomes:**
- HIV-1 RNA <400/<50 copies/ml at 24 and 48 weeks
- HIV-1 RNA ≥400 copies/ml at any of week 4, 8, 12, 24, 36 or 48
- number of HIV-1 mutations present at week 4, 8, 12, 24, 36 or 48 conferring resistance to drugs taken at randomisation or during the trial
- change in CD4 (absolute and percentage) from baseline to 24 and 48 weeks
- change in ART (defined as any change from the ART regimen at randomisation)
- ART-related grade 3 or 4 clinical and laboratory adverse events
- new CDC stage C diagnosis or death
- child and family acceptability of and adherence to twice-daily lopinavir/ritonavir 100/25mg tablets dosed on body weight, over 48 weeks as assessed by patient/carer completed questionnaires
- child and family acceptability of and adherence to once-daily compared to twice-daily dosing of lopinavir/ritonavir tablets, over 48 weeks as assessed by patient/carer completed questionnaires

**Tertiary Outcomes:**
- Tanner Scale at 24 and 48 weeks

### 4.5 Data collection and handling

All data except adherence and acceptability questionnaires, PK and resistance data will be recorded on case report forms (CRFs); the top copy/original should be sent to the appropriate Trials Unit for data entry and a copy kept at the local centre. The type of data to be recorded is detailed in the Assessments section (section 8). Data from the CRFs will be entered onto databases held at the coordinating Trials Units, and exported into Stata for analysis. After completion, adherence and acceptability questionnaires should be sent to the appropriate Trials Unit for data entry. A copy of these questionnaires should be kept in the patient's files at the site. PK data will be entered into excel spreadsheets and exported into WinNonlin for PK analysis. Resistance data will be sent to the Trials Units in the form of sequences (fasta files), entered onto the databases and interpreted according to the latest version of the of the Stanford HIVdb algorithm.

### 5 SELECTION OF CHILDREN

#### 5.1 Inclusion criteria
- aged <18 years (up to 18th birthday) with confirmed HIV-1 infection
- weight ≥15 kg
- able to swallow tablets
- stable (i.e. CD4 not declining) on a combination antiretroviral regimen that has included lopinavir/ritonavir for at least 24 weeks
- taking lopinavir/ritonavir dosed twice-daily and be willing at the screening visit to change to tablet formulation (if not currently taking tablets) and to change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.2); if participating in the PK study*, be willing at the screening visit to change to lopinavir/ritonavir half strength formulation tablets (100/25mg) only, dosed twice-daily and change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.1)
- most recent HIV-1 RNA viral load <50 copies/ml, and viral suppression for the previous 24 weeks. Where viral suppression is defined as HIV-1 RNA <50 copies/ml, with the exception of a single measurement ≥50 but <400 copies/ml
- children and caregivers willing to participate in the PK study if they are among a minimum of 16 children enrolled in each body weight band in the trial, including a second PK assessment if randomised to switch to once-daily lopinavir/ritonavir.
- parents/carers and children, where applicable, give informed written consent

* a minimum of 16 children per weight band will be entered into the PK study and must be willing to change to taking half-strength formulation lopinavir/ritonavir tablets (100/25mg)
only, dosed according to the FDA recommended dosing plan based on their body weight, at the screening visit. Once it has been confirmed that evaluable PK data have been obtained for each weight band on twice- and once-daily dosing, it will no longer be necessary for children entering the trial to take half strength formulation lopinavir/ritonavir tablets only.

5.2 Exclusion criteria
- children on an antiretroviral regimen that includes a NNRTI or any PI other than lopinavir/ritonavir
- children who have previously failed virologically on a PI containing regimen (where virological failure is defined as two successive HIV-1 RNA results > 1000 copies/ml (confirmed) more than 24 weeks after starting HAART, i.e. changes for toxicity are not counted as failure)
- acute illness
- abnormal renal or liver function (grade 3 or above)
- receiving concomitant therapy except for prophylaxis; Some treatments may be allowed, but must first be discussed with a trial medical expert
- pregnancy or risk of pregnancy in females of child bearing potential

5.3 Co-enrolment guidelines
Co-enrolment in compatible studies is allowed by the protocol but must first be approved by the Trials Unit. Centres should also adhere to local guidelines concerning co-enrolment in other trials.

5.4 Number and source of children
It is planned to recruit 160 children from clinical centres in countries participating in the PENTA, HIV NAT (Thailand) and PHPT (Thailand) networks. A minimum of 16 children enrolled in each body weight band (≥15 to ≤25kg, >25 to ≤35kg, >35kg) will participate in the pharmacokinetic study. As of 16th November 2010, in order to ensure representativeness of the study population, no more than 50% of children from the same country should be enrolled within each weight band in the PK study. In countries which have already recruited more than 50% of the children in a given weight band subsequent participants from that country will be enrolled in the main part of the study without PK sampling.

6 ENROLMENT AND RANDOMISATION

6.1 Screening procedure and pre-randomisation investigations

6.1.1 Enrolment and consent
Before approaching the patient about participation in the trial, investigators should contact the coordinating Trials Unit to inform them about a possible eligible patient. The Trials Unit will let you know whether your patient should be entered into the PK study. There are separate information sheets for the PK study and for subsequent enrolments (no PK).

Children should be allowed to enter the trial only if they meet all eligibility criteria (see section 5.1 and 5.2) and are taking a lopinavir/ritonavir-containing HAART regimen.

All parents/guardians and children (where applicable) will be given information about the objectives and rationale of the trial and the possible risks (see sample patient information sheets in Appendix 1).

Written informed consent to enter the trial must be obtained from parents/guardians (including legal authorities) after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial (see
sample consent form - Appendix 2). All children who are deemed competent by the paediatrician and are aware of their HIV diagnosis will be given an age-specific information sheet (see Appendix 1) and asked to sign an assent form (see Appendix 3). For 16-17 year olds, consents should be obtained following national regulations (see Appendix 2).

It must be made completely and unambiguously clear to parents and participants that they are free to refuse to participate in the trial, or withdraw their consent at any time and for any reason, without incurring any penalty or affecting their treatment. Parents/guardians and potential participants can consider entry into the trial for as long as they require, as long as the eligibility criteria are still met.

The signed informed consent form must be kept in the trial site file with a copy in the patient’s medical records and one given to the family/participant. With the parents' and/or participant’s consent, a letter should be sent to the general practitioner (GP) informing him/her of the trial and the participant’s involvement in it (see Appendix 4).

**Once informed consent has been obtained**, the child’s trial number should be allocated from the list of trial ID numbers provided in the site file. This number should be used on all trial-related forms and should be entered on the trial register.

6.1.2 Screening visit - general

The screening visit should not take place less than 2 weeks before randomisation* and ideally no more than 4 weeks before.

*unless there is no need to change the dose nor the formulation of lopinavir/ritonavir at the screening visit

A clinical assessment should be completed which will include measurement of height and weight and the participant and/or carer (according to age and knowledge of HIV diagnosis) should complete an adherence questionnaire (see flowsheet in section 1.8).

A pregnancy test should be performed for all females of childbearing potential within 72 hours of enrolment and the results must be received before randomisation. The pregnancy test can be either a urine sample or blood sample test (HCG). If the pregnancy test is positive, the female will no longer meet the inclusion/exclusion criteria (section 5.1/5.2) and should not be randomised.

Blood will be taken for haematological and biochemical investigations, T-cell subsets measurement of HIV-1 RNA viral load (the same assay should be used throughout the trial at each assessment, although the assays used may vary across centres according to clinical practice and management). An additional 8ml should be drawn in EDTA for a single PK level (measured retrospectively) and plasma storage. Time of last intake of medication will be recorded.

As soon as the biochemistry and immunological/virological results are received and eligibility has been confirmed, the Screening Form with confirmation of eligibility and receipt of informed consent, clinical history and assessment, ART history and prescription, haematology, biochemistry and HIV-1 RNA viral load should be faxed to the Trials Unit.

Lopinavir/ritonavir should be changed to tablet formulation if the child is not already taking tablets and the current dose of lopinavir/ritonavir (twice-daily) should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.2 or 7.2.1 if participating in the PK study (see section 6.1.3)).
The next clinic visit (week 0) should be scheduled within 2-4 weeks of the screening visit, shortly after the expected receipt date of the HIV-1 RNA viral load and CD4 cell count results from the screening visit. All children should be fasting at this visit.

### 6.1.3 Screening visit – PK study only
Children in the PK study should have drugs dispensed at the screening visit and be asked to bring remaining drug back at week 0 for a pill count. Children should be prescribed lopinavir/ritonavir half strength formulation tablets (100/25mg) only, given twice-daily, and the current dose of lopinavir/ritonavir should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.1). It should be explained to carers/children that the evening dose of lopinavir/ritonavir tablets should be taken 12 hours (+/- maximum of 2 hours) before the 1st blood draw (time 0) on the week 0 PK day. The suggested time for intake and arrival at clinic should be written on the pre-PK information sheet (Appendix 7). Carers/children should be asked to record accurately on this sheet the time of the evening doses on the day before the week 0 PK day and should be told not to take their morning dose of antiretrovirals before they come to clinic on the PK day.

### 6.2 Week 0 visit and randomisation procedure

#### 6.2.1 All participants
The eligibility criteria and consent should be re-confirmed verbally and noted on the Randomisation form. If the parents and/or participant are prepared for once-daily lopinavir/ritonavir to commence at this visit, telephone or fax the randomisation form to the appropriate Trials Unit (see main contact details) to randomise the participant. The Trials Unit will assign the child to either continue the same HAART regimen with lopinavir/ritonavir tablets taken twice-daily (BID arm) or to continue the current HAART regimen but switch to lopinavir/ritonavir tablets dosed once-daily (OD arm). For children in the PK study, the PK assessment should be underway before the child is randomised.

A clinical assessment should be completed which includes measurement of height, weight, tanner scales, recording of ethnic origin, presence of adverse events and change in HIV disease stage (including clinical lipodystrophy). The following investigations are to be performed: haematology, biochemistry, lipid profile (fasting), measurement of HIV-1 RNA viral load, T cell subsets and glucose.

Carers and children, as appropriate, should complete an adherence questionnaire. For children in the PK study, the adherence questionnaire should be completed before any blood is taken.

Blood should be taken for plasma storage and for a single PK level in the children not in the PK study. Time of last intake of medication will be recorded.

An acceptability questionnaire should also be completed before the carer or young person knows whether they have been randomised to once- or twice-daily dosing (see flowsheet in section 1.8). The paediatrician should complete the Trial entry form and fax or send to the Trials Unit, together with the completed questionnaires, once all the laboratory results are available.

A full clinic visit should be scheduled for 4 weeks after the week 0 visit (week 4 visit).

#### 6.2.2 BID arm
The children in the BID arm will remain on BID lopinavir/ritonavir for the rest of the trial.
6.2.3 OD arm
The children in the OD arm should switch to OD lopinavir/ritonavir, whilst keeping the same total daily dose. Children should take their BID evening dose as usual on the day of the week 0 visit and start taking their lopinavir/ritonavir once a day from the following day (in the morning if in the PK study (see section 6.2.5)).

Children should continue to take once-daily lopinavir/ritonavir unless the clinician or the family have concerns which they should discuss with the relevant Trials Unit.

Children NOT participating in the PK study may also simplify other antiretrovirals in the regimen to OD at week 0 if appropriate. Children in the PK study should wait until after the PK day at week 4 before simplifying other antiretrovirals in the regimen to OD.

6.2.4 PK study only – week 0 PK day
A minimum of 16 children enrolled in each weight band will undergo a full PK assessment on twice-daily half strength lopinavir/ritonavir tablets at week 0. Children should come to the clinic fasting and without having taken the morning dose of antiretrovirals, and should bring the bottle of tablets dispensed at the screening visit so a pill count can be performed. The pre-PK information sheet, adherence questionnaire and pill count should be reviewed and the PK assessment delayed if there are concerns about adherence.

2ml of blood should be taken at times 0h (trough level before taking morning antiretrovirals), 2h, 4h, 6h, 8h and 12h (trough level before evening dose). Times of blood draws, meals and medications will be recorded on the CRF. The first blood sample should be taken before the child has breakfast. Standard meals will be provided during the PK day.

6.2.5 PK study, OD arm only – preparation for PK day at week 4
Children should take their BID evening dose as usual on the day of the randomisation visit, after the 12h blood sample has been taken, and start taking their daily lopinavir/ritonavir once a day in the morning from the following day. Children will be allowed to change the time of intake of the OD dose AFTER completion of the PK assessment at week 4 (see section 8.2).

Children should have drugs dispensed at the randomisation visit and be asked to bring remaining drug back at week 4 for a pill count. Children should be prescribed lopinavir/ritonavir half strength formulation tablets (100/25mg) only, given once-daily (in the morning), and the current dose of lopinavir/ritonavir should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.3). It should be explained to carers/children that the morning dose of lopinavir/ritonavir tablets on the eve of the PK day should be taken 24 hours (+/- maximum of 2 hours) before the 1st blood draw (time 0) on the week 4 PK day. The suggested time for intake and arrival at clinic should be written on the pre-PK information sheet (Appendix 7). Carers/children should be asked to record accurately on this sheet the time of the morning doses on the day before the week 4 PK day. They should not have taken their morning antiretrovirals when they come in to the clinic at week 4 and should be fasting (i.e. not have had breakfast).
7 TREATMENT OF PATIENTS

7.1 Lopinavir/ritonavir
Abbott manufactures lopinavir/ritonavir (Kaletra) tablets. Active substances are lopinavir and ritonavir.
- Half-strength tablets contain 100mg lopinavir and 25mg ritonavir; 60 tablets per bottle.
- Full-strength tablets contain 200mg lopinavir and 50mg ritonavir; 120 tablets per bottle.

The other ingredients are:
**Tablet:** Colloidal anhydrous silica, copovidone, sodium stearyl fumarate, sorbitan laurate.
**Tablet coating:** Polyvinyl alcohol, talc, titanium dioxide, macrogols type 3350, yellow ferric oxide E172.

Tablets should be swallowed whole and should not be chewed, broken or crushed.

The guidelines in this protocol are in line with manufacturer’s recommendations at the time of writing, but SPCs are updated from time to time. Up-to-date SPCs are posted on the EMEA website (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000368/WC500039043.pdf) and in line with FDA recommendations which are posted in the FDA website: (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=KALETRA)

7.2 Dosing
Children in the PK study randomised to continue twice-daily dosing of lopinavir/ritonavir should take only half strength tablets (7.2.1) until after their PK assessment at week 0. Children in the PK study randomised to switch to once-daily dosing should take only half strength tablets in the morning (7.2.3) until after their second PK assessment at week 4. A mixture of half-strength and full strength lopinavir/ritonavir tablets can be taken at other times and by other patients (7.2.2 BID arm, 7.2.4 OD arm). See 7.2.5 for a summary.

7.2.1 Twice-daily, half strength formulation tablets only

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose/number of 100/25mg (H) tablets</th>
<th>Dose/number of 100/25mg (H) tablets</th>
<th>Total number of 100/25mg (H) tablets per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 to ≤25</td>
<td>200/50mg 2H</td>
<td>200/50mg 2H</td>
<td>4H</td>
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<tr>
<td>&gt;25 to ≤35</td>
<td>300/75mg 3H</td>
<td>300/75mg 3H</td>
<td>6H</td>
</tr>
<tr>
<td>&gt;35</td>
<td>400/100mg 4H</td>
<td>400/100mg 4H</td>
<td>8H</td>
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7.2.2 Twice-daily, half strength formulation tablets and/or full tablets

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose/number of tablets (H=100/25mg, F=200/50mg)</th>
<th>Dose/number of tablets (H=100/25mg, F=200/50mg)</th>
<th>Total number of tablets per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 to ≤25</td>
<td>200/50mg 2H or 1F</td>
<td>200/50mg 2H or 1F</td>
<td>4H or 2F</td>
</tr>
<tr>
<td>&gt;25 to ≤35</td>
<td>300/75mg 3H or 1F, 1H</td>
<td>300/75mg 3H or 1F, 1H</td>
<td>6H or 2F, 2H</td>
</tr>
<tr>
<td>&gt;35</td>
<td>400/100mg 4H or 2F</td>
<td>400/100mg 4H or 2F</td>
<td>8H or 4F</td>
</tr>
</tbody>
</table>

7.2.3 Once-daily, half strength formulation tablets only

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose/number of 100/25mg (H) tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 to ≤25</td>
<td>400/100mg 4H</td>
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<tr>
<td>&gt;25 to ≤35</td>
<td>600/150mg 6H</td>
</tr>
<tr>
<td>&gt;35</td>
<td>800/200mg 8H</td>
</tr>
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### 7.2.4 Once-daily, half strength formulation tablets and/or full tablets

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose/number of tablets (H=100/25mg, F=200/50mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 to ≤25</td>
<td>400/100mg 4H or 2F</td>
</tr>
<tr>
<td>&gt;25 to ≤35</td>
<td>600/150mg 6H or 3F</td>
</tr>
<tr>
<td>&gt;35</td>
<td>800/200mg 8H or 4F</td>
</tr>
</tbody>
</table>
7.2.5 Strength of tablets, timing and simplifying other antiretrovirals to OD

<table>
<thead>
<tr>
<th></th>
<th>Children in PK Study</th>
<th>Children NOT in PK study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>Strength of tablets</td>
<td>Half strength only until after PK assessment at week 0</td>
<td>Half strength only until after PK assessment at week 4</td>
</tr>
<tr>
<td>Timing</td>
<td>am/pm</td>
<td>am until after PK assessment at week 4</td>
</tr>
<tr>
<td>Other antiretrovirals</td>
<td>Continue with same</td>
<td>Can simplify to OD at week 4, if appropriate</td>
</tr>
</tbody>
</table>

7.3 Viral load rebound (≥50 copies/ml)

All children with a viral load at or above 50 copies/ml, at any point during the study, will be asked to come back as soon as possible and within 4 weeks for a confirmatory re-test.

If subjects have confirmed HIV-RNA ≥50 copies/ml, assessment of adherence or other factors which may interfere with antiviral efficacy should be undertaken. Consideration should be given to switching OD-dosed subjects to BID therapy, and BID-dosed subjects to alternative treatment options as appropriate.

7.4 Changes to ART during the trial

Standard local practice should be followed, including checking ART doses at every visit and adjusting for height and weight as necessary.

If simplification of the ART regimen is deemed necessary for clinical reasons during follow-up, this may be allowed, but must be discussed with the appropriate Trials Unit. For children randomised to the OD arm, simplification of other antiretrovirals in the regimen to OD is allowed, if appropriate, after the PK day at week 4 for children in the PK study, and at week 0 for children NOT in the PK study.

Switching of all drugs in the current ART regimen should only occur if there is immunological, virological or clinical failure (according to local clinical practice), at which point a new regimen should be chosen. Resistance tests or TDM may be used to inform change of regimen, according to local clinical practice.

7.5 Dispensing of lopinavir/ritonavir

In some countries lopinavir/ritonavir tablets (half strength and/or full strength) will be supplied by Abbott Pharmaceuticals.

In other countries patients will be provided with all lopinavir/ritonavir tablets from commercial stock. Pharmacies will be supplied with prescription logs as well as labels for re-labelling of lopinavir/ritonavir tablets which are prescribed for once-daily dosing. If a child stops OD dosing and resumes BID dosing, the drugs labelled for once-daily use should be returned to the pharmacy. Prescription logs may be monitored during site monitoring visits or may be sent to the Trials Unit as requested. Unused drug should be dealt with according to local procedures.
7.6 Modification of trial treatment
If the larger number of tablets and/or larger dose of lopinavir/ritonavir taken as an OD dose cause recurrent vomiting, the need to return to BID dosing should be discussed with the Trials Unit.

7.7 Management of undesired effects

7.7.1 Lipid elevations
Treatment with lopinavir/ritonavir has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Particular caution should be paid to patients who had high values when initiating lopinavir/ritonavir therapy or have history of lipid disorders. Lipid disorders should be managed as clinically appropriate.

7.7.2 Pancreatitis
Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and lopinavir/ritonavir therapy should be suspended if a diagnosis of pancreatitis is made.

7.7.3 PR and QT Intervals Prolongation
Prolongation of the PR and QT intervals has been reported in some patients. Cases of second or third degree atrioventricular block have been described. Lopinavir/ritonavir should be use with caution in patients with heart or conduction system abnormalities. Clinical monitoring is recommended when lopinavir/ritonavir is co-administered with other drugs that prolong the PR interval. Avoid the use of lopinavir/ritonavir in patients with congenital long QT syndrome, those with hypokalemia or co-administration with drugs that prolong the QT interval.

7.7.4 Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients/carers should be advised to seek medical advice if joint aches and pain, joint stiffness or difficult in movement are experienced.

7.7.5 Gastrointestinal events
The risk of diarrhoea and other gastrointestinal events such as nausea or vomiting may be greater when the daily dose of lopinavir/ritonavir is taken once daily. Close monitoring of these events is recommended and resumption of twice daily dosing should be considered.

Patients with an SAE must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary (see Section 10.2 for notification procedures). Any patient with serious drug related toxicity will need to substitute lopinavir for an alternative boosted PI. This should be discussed with the clinical study team.

Contact the appropriate Trials Unit for advice if a switch from OD to BID or substitution of lopinavir/ritonavir for toxicity is being considered.

7.8 Non-trial treatment

7.8.1 Other antiretrovirals
For the remaining drugs in the HAART regimen, routine supplies of ART will be used and clinic dispensing records kept as usual.
7.8.2 Medications permitted
No concomitant medication apart from prophylactic antibiotics should be taken during the PK study. Medication required for a concurrent illness during the trial should be documented on the appropriate form.

7.8.3 Medication not permitted/precautions
Lopinavir and ritonavir are inhibitors of the P450 isoform CYP3A. Lopinavir/ritonavir should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events: astemizole, terfenadine, oral midazolam, triazolam, cisapride, pimozide, amiodarone, ergot alkaloids (e.g. ergotamine, dihydroergotamine) and vardenafil.

St John's wort (*Hypericum perforatum*) must not be used due to the risk of decreased plasma concentrations and reduced clinical effect of lopinavir/ritonavir.

Simvastatin and lovastatin are not recommended due to increased risk of myopathy & rhabdomyolysis. Caution (and reduced doses) with rosuvastatin and atorvastatin. Pravastatin or fluvastatin recommended.

Phenobarbital, phenytoin, carbamazepine will induce CYP3A4 and may decrease lopinavir concentrations.

Caution with drugs known to induce QT interval prolongation: chlorpheniramine, quinidine, erythromycin, clarithromycin – possible increased concentrations may result in increased cardiac events.

Rifampicin should be avoided unless strictly necessary - causes large decreases in lopinavir levels and may significantly decrease therapeutic effect. Higher doses of lopinavir/ritonavir have been associated with a higher risk of liver and GI toxicity.

7.9 End of trial
Stable and virologically suppressed children who were randomised to once daily kaletra can continue on the once-daily dosing if agreed by the physician, pharmacist and family.

8 ASSESSMENTS AND FOLLOW-UP

Complete details of local laboratory issues, cost issues and logistics are given in the Manual of Operations. Please also refer to the flowsheet in section 1.8 for the specific requirements at each visit.

8.1 Schedule for follow-up
All children will have clinic visits at screening, week 0, 4, 8, 12, 24, 36 and 48, and then every 12 weeks until the last patient randomised reaches 48 weeks.

The paediatrician may request more frequent visits for participants in either arm, if required. The flowsheet in section 1.8 indicates the minimum number of visits for protocol completion and data recording. However it is the investigator’s responsibility to see participants as frequently as necessary, particularly for the monitoring of adverse events.

Participants should be fasting at week 0, 24 and 48 in order to obtain fasting lipids and glucose values.
8.2 Week 4 visit

8.2.1 PK study, OD arm only – week 4 PK day
The children in the PK group randomised to OD lopinavir/ritonavir (minimum 24 children) will have a second full PK assessment at the week 4 visit, as well as a normal clinic visit.

The PK assessment includes a 24h sample and arrangements should be made for the child to stay overnight in hospital or to return for the 24h sample the following morning. Children should not have their morning antiretrovirals when they come into the clinic and should be fasting (i.e. not have had breakfast which will be provided by the clinic).

Carers/children should bring the bottle of tablets dispensed at the randomisation visit so a pill count can be performed. The pre-PK information sheet, adherence questionnaire and pill count should be reviewed and the PK assessment delayed if there are concerns about adherence.

A 2ml blood sample should be taken at times 0h (trough level before taking morning antiretrovirals), 2h, 4h, 6h, 8h and 24h (trough level before following morning dose). Times of blood draws, meals and taking of medication will be recorded on the CRF.

An adherence questionnaire, as appropriate, should be completed before any blood is taken (see section 8.7).

Children will be allowed to change the time of intake of the OD dose to the evening and simplify other antiretrovirals in the regimen to OD, if appropriate, AFTER completion of the week 4 PK day.

8.2.2 BID arm and OD arm not in PK study
Children on BID lopinavir/ritonavir and children on OD lopinavir/ritonavir who were not included in the PK study will have a normal clinic visit including blood stored for a single PK level.

8.3 Clinical examination
A clinical examination must be performed at screening, week 0 and at identified follow-up protocol visits (see flowsheet in section 1.8). At each visit the following should be recorded:
- Body weight and height
- Any adverse event since last protocol visit, including in particular haematological abnormalities, pancreatitis, diarrhoea
- Change in HIV disease stage since last protocol visit (including clinical lipodystrophy)

Tanner scales should be completed, in children >30kg or >9 years of age, at randomisation (week 0) and repeated every 24 weeks until the end of the trial (Appendix 11).

Pregnancy tests should be performed for all females of childbearing potential at screening (week 2 to week 4) and repeated every 24 weeks until the end of the trial and at other timepoints if required. The pregnancy test at screening must be done within 72 hours of enrolment and its results must be received before randomisation. The pregnancy test could be either a urine sample or blood sample test. If a pregnancy test performed during the trial is positive please contact and discuss with the appropriate Trials Unit.

Ethnic origin will be collected as it has been previously reported to be one of the factors that has an impact on the PK parameters and response to treatment.
8.4 **Antiretroviral therapy**
Prescriptions of antiretroviral therapy and any alterations to prescribed doses should be recorded on the CRF. Doses should be checked at every visit and adjusted for weight and height if necessary.

Time of last intake of medication will also be recorded all visits.

8.5 **Laboratory tests**
Laboratory tests for efficacy and safety monitoring will include:

**Haematology:**
- Haemoglobin, MCV, platelets
- White cell count, neutrophil and lymphocyte counts

**Biochemistry:**
- Creatinine, albumin, total bilirubin, ALT (SGOT), AST (SGPT), Alkaline Phosphatase

**Lipids/glucose:**
- (participants should be fasting overnight at week 0, weeks 24 and 48) Triglycerides, cholesterol (total, LDL, HDL, VLDL), glucose

**Lymphocyte subsets:**
- CD3 (absolute and percentage)
- CD3+CD4 (absolute and percentage)
- CD3+CD8 (absolute and percentage)
- Total lymphocyte count (if measured by immunology laboratory)

**Virology:**
- HIV-1 RNA (viral load), using an ultrasensitive assay if possible. It is also planned to do resistance testing on stored samples.

8.6 **Plasma for storage**
8ml of EDTA blood will be collected throughout the trial at required protocol visits (see flowsheet in section 1.8) for plasma storage. 6ml for retrospective HIV or ART related tests as appropriate, including resistance testing. 2 ml for retrospective measurement of single PK level.

For children in the PK study having a full PK assessment at week 0 (and week 4 if randomised to OD), only 6ml of blood will be collected for plasma storage.

8.7 **Adherence and acceptability**
Adherence and acceptability questionnaires should be completed without conferring with friends or relatives and all questions should be answered even if the carer/young person feels them to be irrelevant. The appointed person at the site should check each questionnaire for its completeness, ensuring that the correct date of completion and patient identifiers are present. The Paediatrician/Research Nurse should approach carers/children at appropriate clinical visits to complete a questionnaire.

For children aware of their diagnosis and deemed capable by the paediatrician, a questionnaire should be provided for both the carer and the child. For children unaware of their diagnosis and deemed capable by the paediatrician, only a carer questionnaire should be provided.
8.7.1 Adherence
Carers and children, where appropriate, will be asked to complete adherence questionnaires at screening and weeks 0, 4, 8, 12, 24 and then every 24 weeks.

For children in the PK study having a full PK assessment at week 0 (and week 4 if randomised to OD), the adherence questionnaire should be completed before any blood is taken.

8.7.2 Acceptability
All carers and children, as appropriate, will be asked to complete an acceptability questionnaire at week 0 before the carer or young person knows whether they have been randomised to once- or twice-daily dosing.

For children randomised to once-daily dosing, their carers and the children, where appropriate, will be asked to complete acceptability questionnaires at week 48, or earlier if a child returns to BID dosing (see section 8.8)

8.8 Follow-up of OD arm patients resuming BID dosing.
If a child randomised to the OD arm resumes BID lopinavir/ritonavir, they should be seen at weeks 0 (day of restarting BID) 4, 8, 12 and then every 12 weeks, following the visit schedule in section 1.8. They should complete an acceptability questionnaire when restarting BID lopinavir/ritonavir.

8.9 Procedures for assessing efficacy

8.9.1 Primary outcomes
In order to compare the proportion of children ever recording plasma RNA $\geq 50$ copies/ml (confirmed within 4 weeks) on OD compared to BID therapy over 48 weeks, HIV-1 viral load will be measured at screening, week 0 and at all follow-up protocol visits. If at any time the HIV-1 viral load is $\geq 50$ copies/ml, the family should be contacted so the HIV-1 viral load can be re-measured as soon as possible and within 4 weeks after the raised value.

In order to evaluate the pharmacokinetics of twice-daily lopinavir/ritonavir half strength formulation tablets based on body weight a minimum of 16 children in each weight band ($\geq 15\text{ to }\leq 25kg$, $>25\text{ to }\leq 35kg$, $>35kg$) will have an intensive PK day while on BID half strength formulation (day 0). Plasma concentrations of lopinavir and ritonavir will be determined by a validated high performance liquid chromatography assay with UV detection in a central laboratory (Radboud University Nijmegen).

To compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children, children who have undergone an intensive PK day and have been subsequently randomised to OD dosing will have a second intensive PK day four weeks after starting OD dosing of lopinavir/ritonavir tablets.

8.9.2 Secondary outcomes
The stage of children’s HIV disease by CDC classification (Appendix 8) will be recorded at entry to the trial and at each protocol visit, disease progression will be recorded on the follow-up CRF as well as any adverse events. Efficacy of twice- and once-daily dosing of lopinavir/ritonavir tablets will also be compared through analysis of HIV-1 viral load and T cell subsets measured locally at each protocol visit, and the presence of HIV mutations conferring resistance to drugs taken at randomisation or during the trial.
8.10 Procedures for assessing safety
A clinical examination should be performed at screening, week 0 and at all follow-up protocol visits. At each visit, any adverse event since the last protocol visit should be recorded (see toxicity grading table, Appendix 10). Any event fitting the ICH definition of serious (see section 12.1) should be reported to the Trials Unit on an SAE form within 24 hours or one working day (see section 12.2 for procedure). All other adverse events should be reported on the Follow-up CRF.

Further details on reporting of adverse events are presented in section 12.

8.11 Trial closure

8.11.1 Planned end of trial
The trial will be considered closed after the last patient to be enrolled reaches 48 weeks of follow-up. However, results will not be available for approximately 6 months after the end of the trial once all data have been received and analysed by the Trials Units. The date of the expected end of the trial will be communicated to the participating centres approximately 3-6 months before the trial ends. The sponsor, or the sponsor’s representative in each country, will notify the national regulatory body and ethics committee of the end of the trial. The Principal Investigator at each site will be responsible for notifying Local Ethics boards and any other local bodies, such as R&D departments.

The TSC may decide to continue further observational follow-up of all patients enrolled in the trial. If long term follow-up of the trial is indicated, ethical opinion will be sought.

8.11.2 Archiving of data
Data will be stored for 15 years and will be treated in accordance with the UK Data Protection Act of 1998. Blood samples will be shipped to an ANRS central storage facility in Lyon, France.

9 TRANSFER OF CHILDREN AND WITHDRAWAL

9.1 Participant transfers
For children moving from the site at which they enrolled to a new site, every effort should be made for them to be followed at the new site and for this site to take over responsibility for the patient. If the site was not listed on the initial Clinical Trial Authorisation, an appropriate Principal Investigator will need to be identified and regulatory and ethics approvals obtained at the new site. A set-up visit will be carried out at the new site and copies of all trial-related documents will be provided. The care giver/participant will need to sign a new consent form at the new site. Until this happens, the follow-up of the patient within the trial remains the responsibility of the recruiting site.

9.2 Transition to adult care
Young people recruited at the ages of 16 and 17 must either be in regular physical contact with their paediatrician or be able to transition to an adult physician at the same site for follow-up or have follow-up at an affiliated adult site (where ethics and R&D have been obtained). When a young person becomes 18 (or at an earlier age if required by national regulations) during the trial, they must give consent if this has not been gained previously.
9.3 Withdrawal
Caregivers and young people have the right to withdraw from the allocated intervention at any time for any reason. Should a caregiver decide to withdraw from either the protocol and allocated intervention, from routine follow-up data, or withdraw all data, a complete evaluation should be made with an explanation of why the young person is withdrawing, unless consent is specifically withheld. If clinicians wish to withdraw a young person they should discuss this first with the appropriate Trials Unit.

Wherever possible, participants should continue to be followed for clinical and laboratory assessments and information recorded 12 weekly unless the caregiver and the young person, if appropriate, explicitly withdraw consent for observational follow-up. If possible the 48 week HIV-1 viral load, T-cell subsets and plasma stores should be obtained.

10 SAFETY REPORTING
ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 10.1 lists definitions, section 10.2 gives details of the institution/investigator responsibilities and section 10.3 provides information on the Trials Units’ responsibilities (on behalf of the sponsor).

Please note the changes from previous PENTA protocols on the reporting of HIV-related signs and symptoms: these are now considered AEs or SAEs as appropriate.

10.1 Definitions
The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in the table below.

Table 1: Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (AE)</td>
<td>Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.</td>
</tr>
<tr>
<td>Adverse Reaction (AR)</td>
<td>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</td>
</tr>
<tr>
<td>Unexpected Adverse Reaction (UAR)</td>
<td>An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.</td>
</tr>
</tbody>
</table>
| Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) | Respectively any adverse event, adverse reaction or unexpected adverse reaction that:  
  • results in death  
  • is life-threatening*  
  • requires hospitalisation or prolongation of existing hospitalisation**  
  • results in persistent or significant disability or incapacity  
  • consists of a congenital anomaly or birth defect  
  • other medically important/clinically significant events*** |
*The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures) that has not worsened do not constitute an SAE. Similarly, if an admission is due to a change of HAART regimen, this will not constitute an SAE.

***Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Disease progression which meets the seriousness criteria or death as a result of disease progression is now considered to be SAEs and should be reported as a SAE. They should be graded according to the guidelines in the toxicity table (appendix 10) under ‘Clinical Symptoms not otherwise specified in this table’.

10.2 Institution/Investigator Responsibilities

All SAEs must be reported by the investigator to the Trials Unit on a Serious Adverse Event (SAE) form within one day of the investigator being aware of the event.

All other AEs/ARs should be reported on the regular follow-up forms.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in Appendix 10. A flowchart is given at the end of this section to help explain the notification procedures.

10.2.1 Investigator Assessment

(a) Seriousness
When an AE/AR occurs the investigator/Paediatrician responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 1. If the event is serious, then an SAE form must be completed and the Trials Unit notified.

(b) Causality
The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 2. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

If a drug is at least possibly related to an AE, this should be noted on the follow-up form.
Table 2: Definitions of causality

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
<th>Event Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship</td>
<td>SAE</td>
</tr>
<tr>
<td>Unlikely</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatment).</td>
<td>SAE</td>
</tr>
<tr>
<td>Possible</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).</td>
<td>SAR</td>
</tr>
<tr>
<td>Probable</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
<td>SAR</td>
</tr>
<tr>
<td>Definitely</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
<td>SAR</td>
</tr>
</tbody>
</table>

(c) Expectedness
If the event is a SAR the Investigator must assess the expectedness of the event. If a SAR is assessed as being unexpected it becomes a SUSAR. The definition of an unexpected adverse reaction (UAR) is given in Table 1 and is one not previously reported in the current summary of product characteristics for lopinavir/ritonavir. Please see Appendix 9 for a summary of expected toxicities.

(d) Notification
The appropriate Trials Unit should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the Trials Unit of all SAEs occurring at any time during the trial.

(e) Other notable events
Pregnancy occurring during participation in KONCERT should be reported on an SAE form and sent to the appropriate Trials Unit within one working day of the investigator becoming aware of the pregnancy. An Outcome of Pregnancy form should be completed subsequently.

Notification Procedure:
1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the appropriate Trials Unit as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.

2. Send the SAE form by fax to the appropriate Trials Unit:

- **MRC Clinical Trials Unit**
  - Fax Number: + 44 (0) 20 7670 4814
- **INSERM SC10-US019**
  - Fax Number: + 33 (0) 1 45 59 51 80
- **PHPT**
  - Fax Number: + 66 (0) 5381 4269
Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked ‘follow-up’ and faxing to the appropriate Trials Unit as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and anonymous code only. The patient’s name should not be used on any correspondence.

3. Staff at the institution must notify their local research ethics body of the event (as per the institutions standard local procedure).

10.3 Trials Units’ Responsibilities
The Medical Experts for the trial and the Chief Investigator (or their medically qualified delegates) will review all SAE reports received on behalf of the sponsor. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU, INSERM/ANRS and PHPT are undertaking the duties of trial sponsor for pharmacovigilance in the countries they co-ordinate and are responsible for the reporting of SUSARs and other SARs to the regulatory authorities of countries in which the trial is taking place and the national research ethics committees as appropriate. In certain instances this responsibility will be delegated to a national co-ordinator. All SAEs will also be notified to Abbott Laboratories.

The Trials Units will also keep all investigators informed of any safety issues that arise during the course of the trial.

Trials Units will comply with any further reporting requirements of the countries they co-ordinate.
Figure 1: Safety Reporting Flowchart

Adverse Event

Was the event serious? (refer to protocol section 10.1)
- Resulted in death
- Life-threatening
- Required inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Another important medical condition

No

Causal relationship to protocol medication?

Unlikely Not related

Yes

Definitely Probably Possibly

Was the SAE one of the recognised undesirable effects of the trial medication specified in the protocol or SPC?

No (Unexpected)

SUSAR Complete SAE form and notify Trials Unit within one working day

SAE Complete SAE form and notify Trials Unit within one working day

Notify Trials Unit as specified in the protocol via follow-up CRF
11 STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation
Randomisation (1:1) will be performed centrally by the MRC Clinical Trials Unit, according to a computer-generated randomisation list, using random permuted blocks, stratified by body weight (≥15 to ≤25kg, >25 to ≤35kg, >35kg).

11.2 Outcome measures

11.2.1 Primary Outcomes:
- HIV-1 RNA ≥50 copies/ml (confirmed) at any of week 4, 8, 12, 24, 36 or 48
- AUC, $C_{min}$ and $C_{max}$ values of lopinavir after twice-daily dosing compared to historical adult [1] and paediatric [2] data
- AUC, $C_{min}$ and $C_{max}$ values of lopinavir after once-daily and twice-daily dosing (in the same children)

11.2.2 Secondary Outcomes:
- HIV-1 RNA <400/<50 copies/ml at 24 and 48 weeks
- HIV-1 RNA ≥400 copies/ml at any of week 4, 8, 12, 24, 36 or 48
- number of HIV-1 mutations present at week 4, 8, 12, 24, 36 or 48 conferring resistance to drugs taken at randomisation or during the trial
- change in CD4 (absolute and percentage) from baseline to 24 and 48 weeks
- change in ART (defined as any change from the ART regimen at randomisation)
- ART-related grade 3 or 4 clinical and laboratory adverse events
- new CDC stage C diagnosis or death
- child and family acceptability of and adherence to twice-daily lopinavir/ritonavir 100/25mg tablets dosed on body weight, over 48 weeks as assessed by patient/carer completed questionnaires
- child and family acceptability of and adherence of once-daily compared to twice-daily dosing of lopinavir/ritonavir tablets, over 48 weeks as assessed by patient/carer completed questionnaires

11.2.3 Tertiary Outcomes:
- Tanner Scale at 24 and 48 weeks

11.3 Sample size

11.3.1 Comparison of the proportion of children ever recording plasma RNA ≥50 copies/ml on OD compared to BID therapy
To compare the proportion of children ever recording plasma HIV-1 RNA ≥50 copies/ml (confirmed within 4 weeks) on once-daily lopinavir/ritonavir compared to twice-daily, over 48 weeks, this trial will enrol 160 young people, 80 per arm, over 18 months.

Assuming 90% of children in the twice-daily arm and the once-daily arm maintain HIV-1 RNA <50 copies/ml to week 48, 155 children will provide at least 80% power to exclude a difference of 12% between the two arms (i.e. to exclude suppression rates of less than 78% in the once-daily arm) (one-sided alpha = 0.05) (15). 160 (80 per arm) young people will be enrolled to allow for loss to follow-up (in previous PENTA trials loss to follow-up has been less than 3%).
A non-inferiority margin of 12% was chosen to represent a clinically acceptable difference in the rate of virological suppression <50 copies/ml between the two arms, and to allow the trial to be adequately powered and feasible to conduct based on estimates of available young people followed in PENTA centres across Europe.

**11.3.2 Confirmation of FDA body weight-based dosing recommendations of twice-daily lopinavir/ritonavir 100/25mg tablets**

To confirm FDA body weight-based dosing recommendations of twice-daily lopinavir/ritonavir 100/25mg tablets, **48 children (16 in each weight band)** will be sufficient for estimation of interpatient variability.

Based on plasma lopinavir PK data from an adult study on tablet formulation (internal Abbott data), the estimated variance of $\log_{10}$ AUC for paediatric tablets was approximately 0.2. **48 (16 in each weight band)** children providing plasma lopinavir PK data on twice-daily tablet regimens will provide at least 80% power for the width of the 90% CI for the mean $\log_{10}$ AUC on twice-daily dosing to be less than 0.230 on the $\log_{10}$ scale. For example, the 90% CI for a mean $\log_{10}$ AUC on twice-daily dosing of 90 mg/L.h would be (69, 117), for 100 mg/L.h (77, 130) and for 110 mg/L.h (84, 143).

**11.3.3 Comparison of the pharmacokinetics of twice-daily with once-daily dosing of lopinavir/ritonavir tablets**

To compare the pharmacokinetics of twice-daily with once-daily dosing of lopinavir/ritonavir tablets, **24 children** with a PK assessment on twice-daily dosing and randomised to the once-daily arm would be available.

Based on plasma lopinavir PK data from an adult study comparing capsule and tablet formulation (internal Abbott data), the estimated variance (within person) of change in $\log_{10}$ AUC between capsules and tablets was approximately 0.05. **24 children** providing plasma lopinavir PK data on both twice- and once-daily tablet regimens will provide at least 80% power for the width of the 90% CI for the mean $\log_{10}$ AUC difference between twice- and once-daily dosing to be less than 0.164 on the $\log_{10}$ scale. Therefore, the 90% CI for a GMR of 1 (no difference between twice- and once-daily dosing observed) would be (0.83, 1.21).

**11.3.4 Evaluable PK data**

If a child in the PK study does not complete one or both PK assessments (if randomised to switch to lopinavir/ritonavir tablets dosed once-daily) and have evaluable PK data, further children will be recruited to the PK part of the trial from the relevant body weight band as replacements.

**11.4 Interim Analyses**

The trial will be reviewed by the PENTA Independent Data Monitoring Committee (IDMC). No member of the PENTA Steering Committee or any clinician (investigator) responsible for the clinical care of trial participants may be a member of the IDMC. The IDMC will review the trial in all aspects, including the number of participants to be recruited. It will review data at regular intervals (approximately every 6 months), in strict confidence, considering the findings from other relevant studies, and will advise the KONCERT Steering committee. The IDMC will alert the Steering Committee to stop the trial on efficacy following the Haybittle-Peto rule i.e. if there is both proof beyond reasonable doubt (p-value <0.001 for primary outcome difference) that for all, or for some types of patient, one particular arm is clearly indicated. After completion of the trial, linked
anonymous data files and a report of data up to week 24 on the safety and efficacy in the OD vs. BID arms and all PK data from the study will be sent to the FDA in the USA.

11.5 Analysis Plan
Intention-to-treat analyses will be performed on all randomised participants. Statistical methods include:

- Descriptive statistics for the summary of baseline characteristics
- Fishers exact test and logistic regression models for the analysis of binary outcome variables
- Analysis of variance and linear regression models for the analysis of continuous outcome variables, adjusting for baseline
- Poisson regression for the analysis of the incidence rate of clinical/adverse events
- Log rank test and proportional hazards regression models for the analysis of time to event variables

The incidence rate of clinical/adverse events will be summarised by body system and randomised arm. First events (in terms of time to first event) and all events will be considered.

Major resistance mutations will be defined by the current IAS-USA list.

A full Statistical Analysis Plan (SAP) will be developed as a separate document. More details on the PK analysis are given below.

11.5.1 PK analysis
Plasma concentrations of lopinavir will be determined by a validated high performance liquid chromatography assay with UV detection. Only children with evaluable PK assessment(s) will be included in the PK analysis. PK parameters of lopinavir will be calculated using non-compartment methods with WinNonlin.

11.5.2 Confirmation of FDA body weight-based dosing recommendations of twice-daily lopinavir/ritonavir 100/25mg tablets
All children with an evaluable lopinavir PK assessment on twice-daily dosing will be included in the analysis. Geometric means (GMs) of $AUC_{0-12}$, $Cl/F/kg$, $C_{max}$ and $C_{min}$ will be calculated overall and in each weight band (>15 to ≤25kg, >25 to ≤35kg, >35kg). Overall lopinavir exposure ($AUC_{0-12}$, $C_{max}$ and $C_{min}$) will be described in relation to historical adult (1) and paediatric (2) data of the pharmacokinetics of lopinavir/ritonavir dosed twice-daily. The GMs will be compared between weight bands by carrying out a t-test for independent samples on log-transformed values. If there is evidence for an overall difference between weight bands ($P<0.05$); t-tests for trend and for all pair-wise comparisons between weight bands will be performed. Additionally, GMs will be compared by ethnic origin by carrying out a t-test on log-transformed values, and weight will be considered as a continuous variable, and linear regression of log-transformed values on weight will be performed.

11.5.3 Comparison of the pharmacokinetics of twice-daily with once-daily dosing of lopinavir/ritonavir tablets
All children with 2 evaluable lopinavir PK assessment days will be included in the analysis and within patient ratios of $AUC_{0-24}$, $Cl/F/kg$, $C_{max}$ and $C_{min}$ for OD versus BID will be calculated. Overall GMRs (geometric mean ratios) for OD versus BID will be calculated after log-transformation of the within-patient ratios. 90% CI for the GMR will be calculated using the t-distribution. A GMR with a 90% CI including 1.0 and falling entirely within 0.80-1.25 will be considered as bioequivalence for $AUC_{0-24}$ and $Cl/F/kg$. 

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Lopinavir exposure in these children will also be described in relation to adult data.
12 TRIAL MONITORING

12.1 Risk assessment
A risk assessment has been conducted to assess the impact of trial participation on the rights and safety of patients, and the reliability of trial results. This has guided the development of procedures in the trial with respect to informed consent, confidentiality and trial monitoring.

12.2 Monitoring at the Trials Units
Data received at Trials Units will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a missing data report of the problematic data will be sent to the local site by secure e-mail for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line, dated and initialled. The amended data should be returned to the appropriate Trials Unit and the amended data should also be filed in the notes at site. The Trials Units will send reminders for any overdue and missing data.

12.3 Clinical site monitoring
The agreement with each principal investigator will include permission for trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. Consent from parents/guardians and children, if appropriate, for direct access to data will also be obtained.

Personal medical data may be reviewed at clinical centres by properly authorised individuals from the Trials Units as part of monitoring and/or audit of the trial, but such information will be treated as strictly confidential and will in no circumstances be made publicly available. All clinical centres will be visited at least once during the trial and following data will be validated from source documents:
- eligibility and signed consent
- clinical disease progression to new CDC C event or death
- all HIV-1 RNA viral loads ≥50 copies/ml
- a random sample of clinical records
- a random sample of CD4 measurements
- a random sample of laboratory results
- a random sample of original records of antiretroviral prescriptions (with batch numbers)

12.4 Confidentiality
The young person’s anonymity will be maintained. On all CRFs and specimens, participants must not be identified by their names. The investigator will be asked to keep a separate Confidential Trial Register which matches the participant’s trial number with their names and should be maintained by the investigator in strict confidence and kept for 15 years.
13 ETHICAL CONSIDERATIONS AND APPROVAL

13.1 Ethical approval
KONCERT will be conducted in full conformance with the principles of the current version of the Declaration of Helsinki, and with the local laws and regulations concerning clinical trials.

At each site, one paediatrician (Principal Investigator) will take on overall responsibility for the conduct of the trial.

The protocol, the informed consent documents and the questionnaires will be formally approved by the regulatory authority and the necessary ethics committees in each participating country. Once these have been approved at a national level, the relevant local research ethics committee and local research and development department at each clinical site will be contacted by the MRC CTU, INSERM or PHPT using appropriate national procedures and sites will be supplied with the required documentation for submission of local approvals.

Before each site can start the trial, the Principal Investigator at each site must send a signed copy of the Investigator’s Agreement to Participate, agreeing to the Terms and Conditions of participation in the trial.

Parental/Guardian written consent will be obtained where appropriate (Appendix 2).

All information collected during KONCERT will be confidential. Names will not be used.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment. Patients who become 18 years of age whilst on the trial will be required to sign a consent form if one has not already been signed by them.

13.2 Ethical considerations
- 3 additional visits are required for the trial above the normal 3-monthly clinic visit schedule (screening, week 4 and week 8). This may involve children taking extra time out of school and parents having to take time off work
- Children in the PK group will undergo one (or two if assigned to once-daily lopinavir/ritonavir) 12-hour blood sampling visits at weeks 0 and 4. This may involve an overnight stay prior to blood sampling. This may present problems in terms of taking time out of work, childcare issues for siblings and wellbeing of the children in the trial
- Children not in the PK group and assigned to BID lopinavir/ritonavir will not benefit from the trial directly as the trial will not affect the treatment they are taking, however they may be able to alter their dosing schedule after analysis of the trial
- This is a randomised trial so neither parents nor children nor the paediatrician will be able to chose whether the child is put on once-daily or twice-daily lopinavir/ritonavir
- There is a small risk that the viral load will become detectable for those children randomised on trial. If a raised viral load is confirmed on repeat testing (to be done within 4 weeks) for a participant randomised to once-daily lopinavir/ritonavir consideration should be given to switching OD-dosed subjects to BID therapy, and BID-dosed subjects to alternative treatment options as appropriate
• Although one of the aims of the trial is to investigate the pharmacokinetics of paediatric lopinavir/ritonavir tablets, a minimum of 112 children in the trial will only be enrolled for the BD versus OD efficacy analysis
• Some visits will require fasting overnight before a morning blood sample. Children will be provided with meals.

14 REGULATORY ISSUES

This trial has been registered with competent authorities in participating countries and has been granted a Clinical Trial Authorisation (CTA).

15 INDEMNITY

In consideration of the agreement by the Principal Investigator at each centre to supervise the trial, the PENTA Foundation undertakes to indemnify the Principal Investigator at each PENTA centre and the institutions which participate in the trial and their employees and agents in respect of any claims made against them by any third party which arises out of or as a result of the supervision or conduct of the trial (including any claim arising in respect of the technical procedures described in the protocol which participants would not have been exposed but for their participation in the trial). Full details of the Indemnity agreement and the cover required for each country are given in a separate document. Cover against claims arising from medical negligence is not included.

For UK Sites only

The co-sponsor of the trial in the UK is the Medical Research Council (MRC).

The Medical Research Council ("the MRC") is not insured but it has indemnity arrangements in place such that successful claims would be met from public funding. The likely scenarios in which the MRC might face claims for damages are set out below. The MRC also sets out below instances where it might make ex gratia payments without any admission of liability.

1. The MRC accepts that it might face claims for damages in cases where:

   a) it co-sponsors the research: (that is it has responsibility for securing the arrangements for managing the study including any research carried out by the MRC Clinical Trials Unit); and

   b) the MRC, or any of its employees, or any person formally acting with the MRC’s authority, have been negligent or have failed to adhere to the relevant guidelines/guidance, legislation or procedure on good practice in relation to medical research; and

   c) that negligence or failure to adhere to legislation, etc has caused or has materially contributed to the personal injury suffered by the individual making the claim.

2. In relation to instances where the MRC is the co-sponsor of research the MRC may consider making an ex gratia payment when a significant adverse reaction in the form of a personal injury has occurred which is likely to have been caused by, or materially contributed to, by participation in a research study. In deciding whether to make such a payment, the MRC will not require the
research participant to demonstrate that the personal injury has been caused by a breach of any duty of care that may have been owed by the MRC.

**16 FINANCE**

Research support will be provided to the clinical centres for additional visits, PK days and sample collection. Where authorised by national ethics bodies, payments or vouchers will be given to participants or their families in compensation for the time spent in clinic during the PK substudy.

Drug will be provided from commercial stock or supplied by Abbott Laboratories if required.

**17 DISSEMINATION**

**17.1 Publication**

The KONCERT TMG will be responsible for preparing the manuscript for rapid publication. High priority will be given to this and it would be anticipated that a report would be completed within six months of a decision to stop the trial. The final publication will require the approval of the KONCERT TMG and TSC. No other publications, including all or any part of the results, either written or verbal, will be made before the definitive manuscript has been agreed and accepted for publication without the prior approval of the KONCERT TMG and TSC. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group has published its report.

Responsibility for data analysis and publication for KONCERT will reside within the PENTA network and be governed by PENTA policies.

The trial will be registered with an internationally accepted clinical trials register (controlled-trials.com) and the unique identification number (ISRCTN) allocated to this trial will be attached to all publications resulting from this trial.

**17.2 Feedback to participants**

A PENTA newsletter will be circulated to sites on an annual basis informing all patients of trials currently recruiting and in follow-up. At the end of the study letters will be sent to participants and families to let them know when the trial will be closing.

After the specific trial results are available, an information sheet in lay terms will be provided for every trial participant to explain the results of the trial. This will be distributed to the Principal Investigators at each site so that the paediatrician can go through it with the child and/or parent/carer to explain the outcome of the trial.
18 PROTOCOL AMENDMENTS

Protocol changes made on 25th November 2009 generating Protocol version 1.1
1. Trial name changed to KONCERT
2. agreed to be co-sponsor for UK sites and provide indemnity for UK sites
3. Updated contact details
4. Screening visits scheduled between weeks -2 to -4. (Pages 12 and 14)
5. Measurement of tanner scales, record of presence of adverse events and of change in HIV disease including clinical lipodystrophy assessment at week 0 instead at screening visit (Pages 14, 24 and 25).
6. Exclusion of participants if receiving concomitant therapy except for prophylaxis (Page 23)
7. All PK samples will be analysed in the pharmacology laboratory in Nijmegen,
8. Information added to section 11.4
9. At the end of the study letters will be sent to participants and families
10. Hospital numbers were removed from patient information sheets
11. Sample Consent forms for those aged 16 and over were included.
12. Toxicity gradings table updated to version: December 2004, clarification August 2009
13. Minor corrections

Protocol changes made on 2nd February generating Protocol version 1.2
1. Addition of Greece and Romania
2. RO/RA phenotype will not be analysed
3. Provision of drug supply from ABBOTT for additional countries.
4. Change in the exclusion criteria: Receiving concomitant therapy except for prophylaxis; Some treatments may be allowed, but must first be discussed with a trial medical expert

Protocol changes made on 1st July 2010 generating Protocol version 1.3
1. Updated contact details and typographic errors (adherence questionnaire)
2. Minor clarifications: use of OD rather than QD; number of 200/50mg tablets in a bottle; correction and re-ordering of PIS for consistency
3. Section 2.1 Background: updated
4. Section 5.1 Exclusion criteria: regimens containing two PIs are not allowed
5. Section 7.7 Management of undesired effects: GI events and general management added
6. Section 10 Safety Reporting: expedited reporting of SAEs occurring at any time during the trial; added information on notification of pregnancy; clarification of medical review of SAEs; reporting of SARs to Abbott.
7. Section 11.4 and consent forms: provision of data to week 24 to the FDA
8. Section 16 (and Patient Information sheets in applicable countries): compensation for time spent on PK study days
9. Consent forms and GP letters: study doctor to be informed of any new medicines being considered during the study

Protocol changes made on 4th August 2010 generating Protocol version 1.4
1. Section 10 Safety reporting: reporting of SAEs to Abbott
2. Consent forms: provision of data to Abbott

Protocol changes made on 16th November 2010 generating Protocol version 1.5
1. Sections 8.3 and 6.2: Ethnic origin of participants will be collected
2. Section 5.2 Exclusion of participants taking NNRTI’s
3. Section 5.4 Number and source of children: As of 16th November 2010, in order to ensure representativeness of the study population, no more than 50% of children from the same country should be enrolled within each weight band in the PK study. In countries which have already recruited more than 50% of the children in a given weight band subsequent
participants from that country will be enrolled in the main part of the study without PK sampling.

4. Section 11.5.2 GMs will be compared by ethnic origin by carrying out a t-test on log-transformed values.

**Protocol changes made on 27th May 2011 generating Protocol version 1.6**

1. Updated contact details and members of the TMG and trial statisticians
2. Page 1: Updated funding information
3. Section 1.8 Assessment flowsheet: clarification
4. Section 5.1 Inclusion criteria: most recent HIV-1 RNA viral load <50 copies/ml, and viral suppression for the previous 24 weeks. Where viral suppression is defined as HIV-1 RNA <50 copies/ml, with the exception of a single measurement ≥50 but <400 copies/ml
5. Section 6.1.2: The screening visit should not take place less than 2 weeks before randomisation* and ideally no more than 4 weeks before. Unless there is no need to change the dose nor the formulation of lopinavir/ritonavir at the screening visit.
6. Section 8.3: Tanner scales to be done at randomisation visit instead of at screening visit.

**Protocol changes made on 23rd April generating Protocol version 1.7**

1. Updated countries taking part in the study, contact details and members of the TMG and trial statisticians
2. Section 1.6: Extended duration of the recruitment period
3. Sections 4.4 and 11.2.3: Tanner scores at week 24 and 48 listed as tertiary outcomes. These scores were already being collected at these time points but were not listed as outcomes.
4. Section 7.9: If agreed by physician, pharmacist and family, support by available PK data will not be required to continue taking lopinavir/ritonavir OD provided the participant is stable and virologically suppressed.
5. Sections 8.6 and 8.9.1: Viral load will not be centrally re-tested in samples with >50 copies/ml.
19 REFERENCES

APPENDIX 1: SAMPLE PATIENT INFORMATION SHEETS

Template versions:
I  Parents/carers
II  Young adults (16+ years)
III  Young people (11 to 15 years)
IV  Children (6-10 years)

There are 2 versions of each PIS:
  a) for a minimum of 16 children recruited to each weight band and participating in the PK study
  b) For subsequent children recruited (i.e. not participating in the PK study)

ALL TO BE PRINTED ON LOCALLY HEADED PAPER AND INCLUDE LOCAL REQUIREMENTS
Ia - Parent/carers – Blood sampling study

KONCERT and Blood Sampling study
An information sheet for parents/carers

We would like to invite you and your child to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you and your child. Please take your time to read the information and to discuss it with your friends, relatives and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is KONCERT?
The study that you and your child are being invited to join is called KONCERT. PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children from many countries will take part in this study.

KONCERT is looking at a type of antiretroviral (anti-HIV) medicine called Kaletra which your child is currently taking. The first aim of KONCERT is to find out whether taking Kaletra once-daily rather than twice-daily is safe and effective in children. As you know, it is very important to take antiretroviral medicines every day but it can be very difficult to give them to children several times per day. If medicines can be taken safely once-daily, this may make them easier to give.

The second aim of KONCERT is to get more information about the correct dose of Kaletra to give children. This is done by measuring the level of the medicine in the child’s blood. This information is needed because a new (smaller) Kaletra tablet for children has recently been approved in many countries and it is important to get as much information as possible about this new tablet.

2) Why has my child been chosen?
Your child has been asked to take part because he/she is currently taking Kaletra and because the virus is currently undetectable in your child’s blood. We plan to enrol 160 children in this study.

3) Does my child have to take part?
It is entirely up to you and your child whether or not your child takes part in this study. It is your right to decide not to take part if you wish. If you don’t want to take part, it will not affect your child’s treatment now or in the future in any way.

If you do decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are free to withdraw your child from the study at any time without giving a reason. Withdrawing from the study will not affect your child’s medical care. We hope, however, that if you do withdraw you will let us know why and will allow us to continue follow-up. This will help us when we look at the results of the study.

As part of the study, blood samples will be stored so researchers can learn more about HIV. We hope that if your child did withdraw from the study, you would still allow us to use these samples. If, however, you did not feel that this was appropriate then we would destroy them.

4) What will happen to my child if he/she decides to take part?

Will my child take Kaletra once-daily or twice-daily? At the start of the study your child will be taking the new smaller Kaletra tablets twice-daily. After we have done some tests on the level of Kaletra in the blood, a computer will pick at random whether your child will continue taking Kaletra twice-daily or start taking it once-daily. Neither you nor your doctor will be able to choose which group your child is in. Half of the children in the study will be in the once-daily group, which means that your child will have a 50% chance of taking once-daily Kaletra, and a 50% chance of...
taking twice-daily Kaletra. If your child prefers taking the larger adult tablets, they can change back to these once the blood sampling days are completed.

**How many clinic visits and how long will the study last?** All children in the study will have a screening visit at the start of the study. Once your child has been enrolled, they will have visits at weeks 0, 4, 8, 12 and then every 12 weeks until the study ends. The study will follow your child until all children have completed 48 weeks on the study. At this point the study will end. However, normal clinic visits will continue for routine monitoring of your child’s health.

**Figure 1. The KONCERT design**

5) **What happens at blood sampling visits?** Your child will be asked to come into hospital for a whole day at week 0 of the study. He/she will have 8 blood samples taken during the day (over 12 hours) to test the level of Kaletra in their blood. A local anaesthetic cream will be used to make the skin numb and a thin tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula, so only one needle prick is required.

If your child changes to once-daily Kaletra, he/she will be asked to come back into hospital for a second whole day of blood sampling at week 4. This may require an overnight stay. If your child stays on twice-daily Kaletra, your child will not be required to have a second day of blood sampling.

6) **What happens at clinic visits?** At the clinic visits after the blood sampling days your child’s height and weight will be measured, and the doctor will look for signs of any illnesses. The doctor will also monitor the onset of puberty every 24 weeks as this can sometimes be delayed by HIV infection and we are interested in knowing how treatment affects it. Blood will be collected at each visit and stored for future tests to find out more about the virus.
7) What else does the study involve?
Adherence and Acceptability questionnaires
We are very interested in finding out what children and families feel about the way the study is going and how they are coping with taking the medicines. Therefore during the study we will ask you and your child to complete questionnaires designed to measure adherence to medication and acceptability of the way they are taking their medications. It is important that you answer these questions as openly as possible.

8) What are the possible benefits of taking part?
• The results of the study will give us more information about whether children can take Kaletra once daily instead of twice daily. This knowledge will also benefit other children in future.
• If the study shows that taking once-daily Kaletra is safe, your child might be able to take Kaletra once-daily after the study ends.
• The results of this study will give us more information about the new smaller Kaletra tablets for children. It is very important that we have this information so we can make sure that children are given the correct dose of medication.

9) What are the possible disadvantages of taking part?
• If your child switches from twice-daily to once-daily Kaletra there is a slight risk that the viral load in the blood might increase. If this happens, the virus will have a small chance of becoming resistant to that medicine. This is very unlikely with Kaletra though, and if there is any rebound of the virus then your child may go back to twice daily treatment straight away if your doctor thinks this is the best thing to do. This might happen if your child forgets to take his/her once-daily dose or if the amount of medicine in your child’s blood is not high enough. An extra clinic visit and a blood test would be necessary to ensure that the virus returned to undetectable level.
• If your child’s switches to once daily Kaletra he/she will have a second blood sampling day at week 4. We will need to measure the level of medicine in the blood over 24 hours and so he/she may need to have an overnight stay in hospital or come back early the next day before taking the morning dose.
• If your child is taking the larger Kaletra adult tablet, we will ask him/her to change to the smaller paediatric size tablet. This will increase the number of tablets your child is taking. If your child prefers taking the larger adult tablets, they can change back to these once the blood sampling days are completed.
• Like any other medicines, your child might experience some side effects such as diarrhoea when taking all the Kaletra tablets in one daily dose. Not everyone gets side effects from the medicines and these should improve after few days. We would encourage you to discuss any concerns with your clinic doctor or nurse.

10) Pregnancy and anti-HIV medicines
Some combinations of anti-HIV medicines might harm an unborn child. If your daughter could become pregnant, she must have a pregnancy test before entering the study and she must use effective contraceptives including condoms or other barrier contraception if she is having sexual intercourse. If your son is having sexual intercourse he must use condoms.

11) Who has reviewed the study and who will monitor its progress?
This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. This study has been reviewed and given favourable opinion by a Research Ethics Committee. A second group (the Independent
Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop. Information from these meetings will be summarised in the PENTA Newsletter for families involved in PENTA studies.

12) Is the information in the trial kept confidential?
All information collected during KONCERT will be kept completely confidential and names will not be used. Your child will only be identified using a study number and date of birth. Your child’s hospital notes will only be made available to study staff and confidentiality will be maintained at all times. If the results of this study are reported or published your child’s name will not be used. Data will be archived for 15 years.

13) What happens at the end of the study?
You and your child’s doctor will continue to make decisions about your child’s medicines once the study has finished.

14) What are the arrangements for compensation?
The PENTA Foundation has made arrangements for compensation if your child comes to any harm because of being in this study. However, if your child is harmed due to someone’s negligence then you may have grounds for legal action for compensation against the hospital where the negligence occurred, but you may have to pay your legal costs.

15) Who else will be informed about the study?
Your child’s GP will only be informed of his/her participation in the study with your permission. Your hospital doctor is not receiving any payment for carrying out this research. You will be able to claim travel costs for any extra visits which are not normally required for clinical care (e.g. week 0, 4, 8). Your costs on the blood sampling days will also be covered.

16) Who can I contact?
If you have any concerns or other questions about the study or the way it has been carried out, or if your child has an injury or illness during the study, contact either the investigator (Dr. _________________/ PENTA Team Ph. No. here) or the hospital where the study is being carried out:

Dr ...................................... contact number
Dr. ..................................... contact number
Nurse ................................. contact number

Thank you for taking the time to consider this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
Ib - Parent/carers – not in blood sampling study

KONCERT

An information sheet for parents/carers

We would like to invite you and your child to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you and your child. Please take your time to read the information and to discuss it with your friends, relatives and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is KONCERT?
The study that you and your child are being invited to join is called KONCERT. PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children from many countries will take part in this study.

KONCERT is looking at a type of antiretroviral (anti-HIV) medicine called Kaletra which your child is currently taking. The first aim of KONCERT is to find out whether taking Kaletra once-daily rather than twice-daily is safe and effective in children. As you know, it is very important to take antiretroviral medicines every day but it can be very difficult to give them to children several times per day. If medicines can be taken safely once-daily, this may make them easier to give.

2) Why has my child been chosen?
Your child has been asked to take part because he/she is currently taking Kaletra and because the virus is currently undetectable in your child’s blood. We plan to enrol 160 children in this study.

3) Does my child have to take part?
It is entirely up to you and your child whether or not your child takes part in this study. It is your right to decide not to take part if you wish. If you don’t want to take part, it will not affect your child’s treatment now or in the future in any way.

If you do decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are free to withdraw your child from the study at any time without giving a reason. Withdrawing from the study will not affect your child’s medical care. We hope, however, that if you do withdraw you will let us know why and will allow us to continue follow-up. This will help us when we look at the results of the study.

As part of the study, blood samples will be stored so researchers can learn more about HIV. We would hope that if your child did withdraw from the study, you would still allow us to use these samples. If, however, you did not feel that this was appropriate then we would destroy them.

4) What will happen to my child if he/she decides to take part?

- Will my child take Kaletra once-daily or twice-daily? A computer will pick at random whether your child will continue taking Kaletra twice-daily or start taking it once-daily. Neither you nor your doctor will be able to choose which group your child is in. Half of the children in the study will be put in the once-daily group, which means that your child will have a 50% chance of taking once-daily Kaletra, and a 50% chance of continuing to take twice-daily Kaletra.

- How many clinic visits and how long will the study last? All children in the study will have a screening visit at the start of the study. Once your child has been enrolled, they will have visits at weeks 0, 4, 8, 12 and then every 12 weeks until the study ends. The study will follow your child until all children have completed 48 weeks on the study. At this point...
the study will end. However, normal clinic visits will continue for routine monitoring of your child’s health.

**Figure 1. The KONCERT design**

![Diagram of the KONCERT design]

**What happens at clinic visits?** At the clinic visits your child’s height and weight will be measured, and the doctor will look for signs of any illnesses. The doctor will also monitor the onset of puberty every 24 weeks as this can sometimes be delayed by HIV infection and we are interested in knowing how treatment affects it. Blood will be collected at each visit and stored for future tests to find out more about the virus.

5) **What else does the study involve?**

**Adherence and Acceptability questionnaires**

We are very interested in finding out what children and families feel about the way the study is going and how they are coping with taking the medicines. Therefore during the study we will ask you and your child to complete questionnaires designed to measure adherence to medication and acceptability of the way they are taking their medications. It is important that you answer these questions as openly as possible.

6) **What are the possible benefits of taking part?**

- The results of the study will give us more information about whether children can take Kaletra once daily instead of twice daily. This knowledge will also benefit other children in future.
- If the study shows that taking once-daily Kaletra is safe, your child might be able to take Kaletra once-daily after the study ends.
7) What are the possible disadvantages of taking part?

- If your child switches from twice-daily to once-daily Kaletra there is a slight risk that the viral load in the blood might increase. If this happens, the virus will have a small chance of becoming resistant to that medicine and therefore the drug will not work as well. This is very unlikely with Kaletra though, and if there is any rebound of the virus then your child may go back to twice daily treatment straight away if your doctor thinks this is the best thing to do. This might happen if your child forgets to take his/her once-daily dose or if the amount of medicine in your child’s blood is not high enough. An extra clinic visit and a blood test would be necessary to ensure that the virus returned to undetectable level.

- Like any other medicines, your child might experience some side effects such as diarrhoea when taking all the Kaletra tablets in one daily dose. Not everyone gets side effects from the medicines and these should improve after few days. We would encourage you to discuss any concerns with your clinic doctor or nurse.

8) Pregnancy and anti-HIV medicines

Some combinations of anti-HIV medicines might harm an unborn child. If your daughter could become pregnant, she must have a pregnancy test before entering the study and she must use effective contraceptives including condoms or other barrier contraception if she is having sexual intercourse. If your son is having sexual intercourse, he must use condoms.

9) Who has reviewed the study and who will monitor its progress?

This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. This study has been reviewed and given favourable opinion by a Research Ethics Committee. A second group (the Independent Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop. Information from these meetings will be summarised in the PENTA Newsletter for families involved in PENTA studies.

10) Is the information in the trial kept confidential?

All information collected during KONCERT will be kept completely confidential and names will not be used. Your child will only be identified using a study number and date of birth. Your child’s hospital notes will only be made available to study staff and confidentiality will be maintained at all times. If the results of this study are reported or published your child’s name will not be used. Data will be archived for 15 years.

11) What happens at the end of the study?

You and your child’s doctor will continue to make decisions about your child’s medicines once the study has finished.

12) What are the arrangements for compensation?

The PENTA Foundation has made arrangements for compensation if your child comes to any harm because of being in this study. However, if your child is harmed due to someone’s negligence then you may have grounds for legal action for compensation against the hospital where the negligence occurred, but you may have to pay your legal costs.
13) **Who else will be informed about the study?**
Your child’s GP will be informed of his/her participation in the study with your permission. Your hospital doctor is not receiving any payment for carrying out this research. You will be able to claim travel costs for any extra visits which are not normally required for clinical care (e.g. week 0, 4, 8).

14) **Who can I contact?**
If you have any concerns or other questions about the study or the way it has been carried out, or if your child has an injury or illness during the study, contact either the investigator (Dr. ________________/ PENTA Team *Ph. No. here*) or the hospital where the study is being carried out:

Dr ................................. contact number
Dr ...................................... contact number
Nurse ............................... contact number

Thank you for taking the time to consider this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
IIa – Young adults – Blood sampling study

KONCERT and Blood sampling study
An information sheet for young adults

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you. Please take your time to read the information and to discuss it with your friends, relatives and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is KONCERT?
The study that you are being invited to join is called KONCERT. PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children and young adults from many countries will take part in this study.

KONCERT is looking at a type of antiretroviral (anti-HIV) medicine called Kaletra which you are currently taking. The first aim of KONCERT is to find out whether taking Kaletra once-daily rather than twice-daily is safe and effective in children. As you know, it is very important to take antiretroviral medicines every day but it can be very difficult to take them several times per day.

The second aim of KONCERT is to get more information about the correct dose of Kaletra to give to children and young adults. This is done by measuring the level of the medicine in your blood. This information is needed because a new (smaller) Kaletra tablet for has recently been approved in many countries and it is important to get as much information as possible about this new tablet.

2) Why are you asking me?
Your have been asked to take part because you are currently taking Kaletra and because the virus is currently undetectable in your blood. We plan to enrol 160 children and young adults in this study.

3) Do I have to take part?
It is entirely up to you whether or not you takes part in this study. It is your right to decide not to take part if you wish. If you don’t want to take part, it will not affect your treatment now or in the future in any way.

If you do decide to take part, we will ask you to sign a consent form to show you have agreed to take part. **You are free to withdraw from the study at any time without giving a reason.** Withdrawing from the study will not affect your medical care. We hope, however, that if you do withdraw you will let us know why and will allow us to continue follow-up. This will help us when we look at the results of the study.

As part of the study, blood samples will be stored so researches can learn more about HIV. We would hope that if you withdrew from the study, you would still allow us to use these samples. If, however, you did not feel that this was appropriate then we would destroy them.

4) What will happen if I decide to take part?

- **Will I take Kaletra once-daily or twice-daily?** At the start of the study you will be taking the new smaller Kaletra tablets twice-daily. A computer will pick at random whether you will continue taking Kaletra twice-daily or start taking it once-daily. Neither you nor your doctor will be able to choose which group you are in. Half of the people in the study will be put in the once-daily group, which means that you will have a 50% chance of taking once-daily Kaletra, and a 50% chance of continuing to take twice-daily Kaletra.
• **How many clinic visits and how long will the study last?** All people enrolled in the study will have a screening visit at the start of the study. Once you have been enrolled, you will have visits at weeks 0, 4, 8, 12 and then every 3 months until the study ends. The study will follow you until all people enrolled in KONCERT have completed 48 weeks on the study. At this point the study will end. However, normal clinic visits will continue for routine monitoring of your health.

**5) What happens at blood sampling visits?**

At the beginning of KONCERT we’ll ask you to come in for a day because we want to look at how well Kaletra stays in your blood. To do this, we will need to take 8 blood samples taken during the day (over 12 hours). A local anaesthetic cream will be used to make the skin numb and a thin tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula, so only one needle prick is required.

The laboratory needs to know exactly when you have taken your Kaletra so you will be asked to record the time of taking Kaletra and your other anti-HIV medicines the day before.

If you are selected to change from twice a day to once a day Kaletra, you will be asked to come back for a second whole day of blood sampling after 4 weeks. This may require an overnight stay. If you stay on twice a day Kaletra, you will not need to come for a second day of blood sampling.

**6) What happens at clinic visits?** At the clinic visits your height and weight will be measured, and the doctor will look for signs of any illnesses. The doctor will also monitor the onset of puberty every 24 weeks as this can sometimes be delayed by HIV infection and we are interested in knowing how treatment affects it. Blood will be collected at each visit and stored for future tests to find out more about the virus.

**7) What else does the study involve?**

**Adherence and Acceptability questionnaires**

We are very interested in finding out what children and families feel about the way the study is going and how they are coping with taking the medicines. Therefore during the study we will ask you and your child to complete questionnaires designed to measure adherence to medication and acceptability of the way they are taking their medications. It is important that you answer these questions as openly as possible.

**8) What are the possible benefits of taking part?**

- The results of the study will give us more information about whether young adults and children can take Kaletra once daily instead of twice daily. This knowledge will also benefit other people in future.
- If the study shows that taking once-daily Kaletra is safe, you might be able to take Kaletra once-daily after the study ends.

**9) What are the possible disadvantages of taking part?**

- If you switch from twice-daily to once-daily Kaletra there is a slight risk that the viral load in the blood might increase. If this happens, the virus will have a small chance of becoming resistant to that medicine and therefore the drug will not work as well. This is very unlikely with Kaletra though, and if there is any rebound of the virus then you may go back to twice daily treatment straight away if your doctor thinks this is the best thing to do. This might happen if you forget to your once-daily dose or if the amount of medicine in your blood is not high enough. An extra clinic visit and a blood test would be necessary to ensure that the virus returned to undetectable level.
• If you are selected to change from twice- to once-daily Kaletra, we will need to measure the level of medicine in your blood over 24 hours and so you may need to have an overnight stay in hospital or come back early the next day before taking the morning dose.

• If you are taking the larger Kaletra tablet, we will ask you to change to the smaller size tablet. This will increase the number of tablets you will need to take. If you prefer taking the larger tablets, you can change back to these once the first blood sampling day is completed.

• Like any other medicines, you might experience some side effects such as diarrhoea when taking all the Kaletra tablets in one daily dose. Not everyone gets side effects from the medicines and these should improve after a few days. We would encourage you to discuss any concerns with your clinic doctor or nurse.

10) Pregnancy and anti-HIV medicines
If you are female, some combinations of anti-HIV medicines might harm an unborn child. If you could become pregnant, you must have a pregnancy test before entering KONCERT. This also means that during KONCERT you need to use effective contraceptives including condoms or other barrier contraception if you are having sex because we wouldn’t want the drugs to harm your unborn child. If you are male you should use condoms too.

11) Who has reviewed the study and who will monitor its progress?
This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. A second group (the Independent Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop. Information from these meetings will be summarised in the PENTA Newsletter for patients and families involved in PENTA studies.

12) Is the information in the trial kept confidential?
All information collected during KONCERT will be kept completely confidential and names will not be used. You will only be identified using a study number and date of birth. Your hospital notes will only be made available to study staff and confidentiality will be maintained at all times. If the results of this study are reported or published your name will not be used. Data will be archived for 15 years.

13) What happens at the end of the study?
You will continue to take the same treatment unless your doctor advises you to change. Your doctor will continue to make decisions about your medicines once the study has finished.

14) What are the arrangements for compensation?
Your travel will be paid for at weeks 0, 4, 8 and any other extra visits which are not normally required for your clinical care.

If anything happens to you because of the study, the PENTA Foundation has made arrangements for compensation.

15) Who can I contact?
If you and/or your parents have any concerns or other questions about the study or the way it has been carried out; or if you have an injury or illness during the study, contact either the investigator (Dr. ______________/ PENTA Team Ph. No. here) or the hospital where the study is being carried out:

Dr ................................. Contact number
Dr................................. Contact number
Nurse ............................ Contact number

Thank you for taking the time to think about this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
IIb – Young adults – not in blood sampling study

KONCERT

An information sheet for young adults

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you. Please take your time to read the information and to discuss it with your friends, relatives and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is KONCERT?
The study that you are being invited to join is called KONCERT. PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children and young adults from many countries will take part in this study.

KONCERT is looking at a type of antiretroviral (anti-HIV) medicine called Kaletra which you are currently taking. The first aim of KONCERT is to find out whether taking Kaletra once-daily rather than twice-daily is safe and effective in children. As you know, it is very important to take antiretroviral medicines every day but it can be very difficult to take them several times per day.

2) Why are you asking me?
You have been asked to take part because you are currently taking Kaletra and because the virus is currently undetectable in your blood. We plan to enrol 160 children and young adults in this study.

3) Do I have to take part?
It is entirely up to you whether or not you take part in this study. It is your right to decide not to take part if you wish. If you don’t want to take part, it will not affect your treatment now or in the future in any way.

If you decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are free to withdraw from the study at any time without giving a reason. Withdrawing from the study will not affect your medical care. We hope, however, that if you do withdraw you will let us know why and will allow us to continue follow-up. This will help us when we look at the results of the study.

As part of the study, blood samples will be stored so researchers can learn more about HIV. We would hope that if you withdrew from the study, you would still allow us to use these samples. If, however, you did not feel that this was appropriate then we would destroy them.

4) What will happen if I decide to take part?

- Will I take Kaletra once-daily or twice-daily? A computer will pick at random whether you will continue taking Kaletra twice-daily or start taking it once-daily. Neither you nor your doctor will be able to choose which group you are in. Half of the people in the study will be put in the once-daily group, which means that you will have a 50% chance of taking once-daily Kaletra, and a 50% chance of continuing to take twice-daily Kaletra.

- How many clinic visits and how long will the study last? All people enrolled in the study will have a screening visit at the start of the study. Once you have been enrolled, you will have visits at weeks 0, 4, 8, 12 and then every 3 months until the study ends. The study will follow you until all people enrolled in KONCERT have completed 48 weeks on the study. At this point the study will end. However, normal clinic visits will continue for routine monitoring of your health.
• **What happens at clinic visits?** At the clinic visits your height and weight will be measured, and the doctor will look for signs of any illnesses. The doctor will also monitor the onset of puberty every 24 weeks as this can sometimes be delayed by HIV infection and we are interested in knowing how treatment affects it. Blood will be collected at each visit and stored for future tests to find out more about the virus.

5) **What else does the research study involve?**

**Adherence and Acceptability questionnaires**

We are very interested in finding out what you feel about the way the study is going and how YOU are coping with taking the medicines. Therefore during the study we will ask you to complete questionnaires designed to measure adherence to medication and acceptability of the way you are taking your medications. It is important that you answer these questions as openly as possible.

6) **What are the possible benefits of taking part?**

- The results of the study will give us more information about whether young adults and children can take Kaletra once daily instead of twice daily. This knowledge will also benefit other people in future.
- If the study shows that taking once-daily Kaletra is safe, you might be able to take Kaletra once-daily after the study ends.

7) **What are the possible disadvantages of taking part?**

- If you switch from twice-daily to once-daily Kaletra there is a slight risk that the viral load in the blood might increase. If this happens, the virus will have a small chance of becoming resistant to that medicine and therefore the drug will not work as well. This is very unlikely with Kaletra though, and if there is any rebound of the virus then you may go back to twice daily treatment straight away if your doctor thinks this is the best thing to do. This might happen if you forget to your once-daily dose or if the amount of medicine in your blood is not high enough. An extra clinic visit and a blood test would be necessary to ensure that the virus returned to undetectable level.

- Like any other medicines, you might experience some side effects such as diarrhoea when taking all the Kaletra tablets in one daily dose. Not everyone gets side effects from the medicines and these should improve after a few days. We would encourage you to discuss any concerns with your clinic doctor or nurse.

8) **Pregnancy and anti-HIV medicines**

If you are female, some combinations of anti-HIV medicines might harm an unborn child. If you could become pregnant, you must have a pregnancy test before entering KONCERT. This also means that during KONCERT you need to use effective contraceptives including condoms or other barrier contraception if you are having sex because we wouldn’t want the drugs to harm your unborn child. If you are male you should use condoms too.

9) **Who has reviewed the study and who will monitor its progress?**

This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. A second group (the Independent Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop. Information from these meetings will be summarised in the PENTA Newsletter for patients and families involved in PENTA studies.
10) Is the information in the trial kept confidential?
All information collected during KONCERT will be kept completely confidential and names will not be used. You will only be identified using a study number and date of birth. Your hospital notes will only be made available to study staff and confidentiality will be maintained at all times. If the results of this study are reported or published your name will not be used. Data will be archived for 15 years.

11) What happens at the end of the study?
You will continue to take the same treatment unless your doctor advises you to change. Your doctor will continue to make decisions about your medicines once the study has finished.

12) What are the arrangements for compensation?
Your travel will be paid for at weeks 0, 4, 8 and any other extra visits which are not normally required for your clinical care.

If anything happens to you because of the study, the PENTA Foundation has made arrangements for compensation.

13) Who can I contact?
If you and/or your parents have any concerns or other questions about the study or the way it has been carried out; or if you have an injury or illness during the study, contact either the investigator (Dr. ________________/ PENTA Team Ph. No. here) or the hospital where the study is being carried out:

Dr ................................. Contact number
Dr................................. Contact number
Nurse ............................. Contact number

Thank you for taking the time to think about this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you. Please take your time to read the information and to discuss it with your parent(s)/carer(s) and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is a research study?

A research study tests how well new medicines and other treatments work and if they are safe. The studies do this by randomly putting patients who want to be involved, in groups that follow different treatments. The researchers (including your clinic doctor and research nurse) need to collect information about the medicine you are taking that will help to improve health and care for children and young people living with HIV both in this country and abroad. This study is called KONCERT.

2) What is KONCERT?

PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children and young people from many countries will take part in this study.

KONCERT is looking at the (anti-HIV) medicine Kaletra which you are currently taking. KONCERT wants to:
- Find out whether taking Kaletra once a day rather than twice a day is safe and still works.
- To get more information about the right amount of Kaletra people need to take. This is done by measuring the level of the medicine in your blood. This information is needed because a new smaller Kaletra tablet has recently been made.

3) Why are you asking me?

We are asking you to take part in KONCERT because you take Kaletra and because your virus is undetectable (asleep) and your CD4 count (fighter cells) is good. We are asking 160 children and young people to take part in this study.

4) Do I have to take part?

No. It is entirely up to you. Talk to your parents, nurse or someone you trust about being involved. If you don’t want to take part, that is completely fine.

If you do decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are free to pull out from the study at any time without giving a reason. This will not affect your medical care. If you are happy to give us a reason why you have stopped that would be great because it will help us understand why this study didn’t work for you.

As part of the study, blood samples will be stored so researchers can learn more about HIV. If you stopped the study, you can decide whether you are happy for us to keep these to learn more about HIV, or whether you want them destroyed.
5) What will happen if I decide to take part?

At the start you will take the new smaller tablet twice a day. Then we will take your blood and look at the level of Kaletra. A computer program will randomly decide whether you will continue taking Kaletra twice a day or start taking it once a day. Neither you nor your doctor will be able to choose the group you will be in.

Half of the people in the study will be in the once-daily group, which means that you will have a 50% chance of taking once-daily Kaletra, and a 50% chance of taking twice-daily Kaletra.

If you decide to join the study, you will need to come to the clinic every four weeks and then you will go back to three monthly appointments. We will follow you until all participants have completed 48 weeks on the study which is when KONCERT will end.

6) What happens at blood sampling visits?

At the beginning of KONCERT we’ll ask you to come in for a day because we want to look at how well Kaletra stays in your blood. To do this, we will need to take 8 blood samples during the day (over 12 hours). A local anaesthetic cream will be used to make the skin numb and a thin tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula, so only one needle prick is required.

The laboratory needs to know exactly when you have taken your Kaletra so you will be asked to record the time of taking Kaletra and your other anti-HIV medicines the day before.

If you are selected to change from twice a day to once a day Kaletra, you will be asked to come back for a second whole day of blood sampling after 4 weeks and you may need to stay overnight in hospital. If you stay on twice a day Kaletra, you will not need to come for a second day of blood sampling, just a clinic visit.

What happens at following clinic visits?

Each time you come to your clinic appointment, you will have your usual blood tests (CD4s, viral load etc), your height and weight will be measured, and your doctor will look for signs of any illnesses.

The doctor will also monitor signs of puberty every 24 weeks as puberty can sometimes be delayed by HIV infection. Blood will be collected at each visit and stored for future tests to find out more about the virus and about the level of Kaletra in your blood.

7) What else does the research study involve?

We are very interested in finding out how you feel about the way the study is going and about taking the medicines. So we will ask you to complete questionnaires at clinic visits. The questions will take less than 10 minutes to complete and will just ask what its like to take the medicine.
8) Pro’s and Cons involved

Pro’s

- We will be able to get lots of information on what is like to take Kaletra once daily instead of twice daily. It could mean that children and young people all over the world living with HIV could benefit.
- We’ll also learn more about the smaller Kaletra tablets. It is very important that we have this information so we can make sure that children are given the correct dose of medication.
- If the study shows that taking once-daily Kaletra is safe, you might be able to take it once-daily after the study ends.

Cons

- If you change treatment from twice-daily to once-daily Kaletra there is a slight risk that the viral load (amount of virus in your blood) will increase. This can also happen if you forget to take your medication everyday or if the amount of medicine in your blood is not high enough. If this is the case, the virus will have a greater chance of becoming resistant to that drug and therefore the drug will not work as well. This is very unlikely with Kaletra though. If your HIV viral load increases, then you may go back to twice daily treatment if your doctor thinks this is the best thing to do. An extra clinic visit and a blood test would be necessary just to check your virus returned to undetectable level.
- If you are taking the larger Kaletra adult tablet, we would ask you to change to the new smaller size tablet. This would increase the number of tablets you are taking. If you prefer taking the larger tablets, you can change back to these once the blood sampling days are completed.
- If you change to once daily Kaletra you will have a second blood sampling day. We need to measure the level of Kaletra in your blood over 24 hours so you may need to stay in hospital overnight or come back early the next day before taking your morning dose.
- If you are taking all your Kaletra in once a day, there is also a small chance you could get an upset stomach and diarrhoea. This generally last only a few days before you feel better again. Not everyone gets side effects from medicines. Some people don’t even get any at all. If you experience any side effects from the medicine, your doctor can give you some other medicine to take with the anti-HIV drugs that will stop or reduce side effects from happening.

9) Pregnancy and anti-HIV medicines

If you are female, some combinations of anti-HIV medicines might harm an unborn child. If you could become pregnant, you must have a pregnancy test before entering KONCERT. This also means that during KONCERT you need to use effective contraceptives including condoms or other barrier contraception if you are having sex because we wouldn’t want the drugs to harm your unborn child. If you are male you should use condoms too.

10) Who has reviewed the study and who will monitor its progress?

This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. This study has been reviewed.
and given approval by a Research Ethics Committee. A second group of independent scientists (the Independent Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop.

11) Is the information in KONCERT kept confidential?

**All information collected during KONCERT will be kept completely confidential and names will not be used.** You will only be identified using a study number and date of birth. Your hospital notes will only be made available to PENTA staff and confidentiality will be maintained at all times. If the results of this study are reported or published, your name will not be used. All the information gathered will be kept securely for 15 years and then destroyed.

If you give permission, your GP will only be informed of your participation in the study.

12) What happens at the end of the study?

You will continue to take the same treatment unless your doctor advises you to change. Your doctor will continue to make decisions about your medicines once the study has finished.

13) What are the arrangements for compensation?

Your travel will be paid for at weeks 0, 4, 8 and any other extra visits which are not normally required for your clinical care.

If anything happens to you because of the study, the PENTA Foundation has made arrangements for compensation.

14) Who can I contact?

If you and/or your parents have any concerns or other questions about the study or the way it has been carried out; or if you have an injury or illness during the study, contact either the investigator (Dr. ________________/ PENTA Team Ph. No. here) or the hospital where the study is being carried out:

Dr. ___________________ Contact number
Dr. ___________________ Contact number
Nurse ________________ Contact number

Thank you for taking the time to think about this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
IIIb – Young people – not in blood sampling study

KONCERT
An information sheet for young people

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why we want to carry out this study and what it will mean for you. Please take your time to read the information and to discuss it with your parent(s)/carer(s) and your doctor or nurse. Please ask if you need more information or if anything is not clear. Take as much time as you need to decide whether or not you wish to take part.

1) What is a research study?

A research study tests how well new medicines and other treatments work and if they are safe. The studies do this by randomly putting patients who want to be involved, in groups that follow different treatments. The researchers (including your clinic doctor and research nurse) need to collect information about the medicine you are taking that will help to improve health and care for children and young people living with HIV both in this country and abroad. This study is called KONCERT.

2) What is KONCERT?

PENTA is an independent organisation that looks at treatment of children and young people with HIV. Children and young people from many countries will take part in this study.

KONCERT is looking at the (anti-HIV) medicine Kaletra which you are currently taking. KONCERT wants to find out whether taking Kaletra once a day rather than twice a day is safe and still works.

3) Why are you asking me?

We are asking you to take part in KONCERT because you take Kaletra and because your virus is undetectable (asleep) and your CD4 count (fighter cells) is good.

We are asking 160 children and young people to take part in this study.

4) Do I have to take part?

No. It is entirely up to you. Talk to your parents, nurse or someone you trust about being involved. If you don’t want to take part, that is completely fine.

If you do decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are free to pull out from the study at any time without giving a reason. This will not affect your medical care. If you are happy to give us a reason why you have stopped that would be great because it will help us understand why this study didn’t work for you.

As part of the study, blood samples will be stored so researchers can learn more about HIV. If you stopped the study, you can decide whether you are happy for us to keep these to learn more about HIV, or whether you want them destroyed.

5) What will happen if I decide to take part?

We will take your blood and look at the level of Kaletra. A computer program will randomly decide whether you will continue taking Kaletra twice a day or start taking it once a day. Neither you nor your doctor will be able to choose the group you will be in.
Half of the people in the study will be in the once-daily group, which means that you will have a 50% chance of taking once-daily Kaletra, and a 50% chance of taking twice-daily Kaletra.

If you decide to join the study, you will need to come to the clinic every four weeks and then you will go back to three monthly appointments. We will follow you until all participants have completed 48 weeks on the study which is when KONCERT will end.

**What happens at clinic visits?**

Each time you come to your clinic appointment, you will have your usual blood tests (CD4s, viral load etc), your height and weight will be measured, and your doctor will look for signs of any illnesses

The doctor will also monitor any signs of puberty every 24 weeks as puberty can sometimes be delayed by HIV infection. Blood will be collected at each visit and stored for future tests to find out more about the virus and about the level of Kaletra in your blood.

6) **What else does the research study involve?**

We are very interested in finding out how you feel about the way the study is going and about taking the medicines. So we will ask you to complete questionnaires at clinic visits. The questions will take less than 10 minutes to complete and will just ask what its like to take the medicine.

7) **Pro’s and Cons to be involved**

**Pro’s**

- We will be able to get lots of information on what is like to take Kaletra once daily instead of twice daily. It could mean that children and young people all over the world living with HIV could benefit.
- If the study shows that taking once-daily Kaletra is safe, you might be able to take it once-daily after the study ends.

**Cons**

- If you have changed treatment from twice-daily to once-daily Kaletra there is a slight risk that the viral load (amount of virus in your blood) will increase. This can also happen if you forget to take your medication everyday or if the amount of medicine in your blood is not high enough. If this is the case, the virus will have a greater chance of becoming resistant to that drug and therefore the drug will not work as well.
  This is very unlikely with Kaletra though. If your HIV viral load increases, then you may go back to twice daily treatment if your doctor thinks this is the best thing to do. An extra clinic visit and a blood test would be necessary just to check your virus returned to undetectable level.

- If you are taking all your Kaletra in once a day, there is also a small chance you could get an upset stomach and diarrhoea. This generally last only a few days before you feel better again. Not everyone gets side effects from medicines. Some people don’t even get any at all. If you experience any side effects from the medicine, your doctor can give you some other medicine to take with the anti-HIV drugs that will stop or reduce side effects from happening.
8) Pregnancy and anti-HIV medicines

If you are female, some combinations of anti-HIV medicines might harm an unborn child. If you could become pregnant, you must have a pregnancy test before entering KONCERT. This also means that during KONCERT you need to use effective contraceptives including condoms or other barrier contraception if you are having sex because we wouldn’t want the drugs to harm your unborn child. If you are male you should use condoms too.

9) Who has reviewed the study and who will monitor its progress?

This study has been looked at by an independent group of people (a Research Ethics Committee) who protect the safety, rights, wellbeing and dignity of participants. This study has been reviewed and given approval by a Research Ethics Committee. A second group of independent scientists (the Independent Data Monitoring Committee) will meet regularly during the trial and will recommend whether the trial should continue as planned or should stop.

10) Is the information in KONCERT kept confidential?

All information collected during KONCERT will be kept completely confidential and names will not be used. You will only be identified using a study number and date of birth. Your hospital notes will only be made available to PENTA staff and confidentiality will be maintained at all times. If the results of this study are reported or published, your name will not be used. All the information gathered will be kept securely for 15 years and then destroyed. If you give permission, your GP will only be informed of your participation in the study.

11) What happens at the end of the study?

You will continue to take the same treatment unless your doctor advises you to change. You and your doctor will continue to make decisions about your medicines once the study has finished.

12) What are the arrangements for compensation?

Your travel will be paid for at weeks 0, 4, 8 and any other extra visits which are not normally required for your clinical care.

If anything happens to you because of the study, the PENTA Foundation has made arrangements for compensation.

13) Who can I contact?

If you and/or your parents have any concerns or other questions about the study or the way it has been carried out; or if you have an injury or illness during the study, contact either the investigator (Dr. ________________/ PENTA Team Ph. No. here) or the hospital where the study is being carried out:

Dr ................................. Contact number
Dr................................. Contact number
Nurse .............................. Contact number

Thank you for taking the time to think about this study. Please ask any questions and let us know if there are things that you do not understand or would like more information about.
KONCERT
An information sheet for children

We would like to invite you to take part in our research study. Before you decide, please take your time to read this information sheet and ask your parents and your doctor or nurse if there is something you don’t understand.

1) What is a research study?

A research study tests how well new medicines and other treatments work and if they are safe to use in people. A group of researchers (including your clinic doctor and research nurse) need to collect information about the medicines you are taking. This will help to improve health and care for children and young people living with HIV who need to take the same medicine. The research study you are being invited to join is called KONCERT.

2) What is the KONCERT research study?

KONCERT is organised by a European group called PENTA. KONCERT is a study for children who are doing really well on their anti-HIV medicines. Children from many European countries will take part in this study.

As you know, it is very important to take your anti-HIV medicines every day but sometimes it can be difficult to take them several times a day. If medicines can be given once a day without any problems, this may make them easier to take. We would like to know if it is safe to take Kaletra once a day instead of twice a day in children.

We also want to get more information on how much of this medicine children should take. This is done by measuring the level of Kaletra in your blood. The blood test will also tell us if your virus stays asleep and your CD4 count (fighter cells) remains high.

3) Why have I been chosen?

You have been chosen to take part in KONCERT because you are taking Kaletra everyday and because your virus is undetectable (asleep) and your CD4 count (fighter cells) is good. We will ask 160 children to take part in this study.

4) Do I have to take part?

It is up to you and your parents whether or not you take part in this study. It is OK if you do not want to take part.
If you decide to take part, you can stop the study at any time without giving a reason and your doctor will still look after you as normal. If you do stop, we would like to know why so we can make the next study better.

5) What happens in the study?

All children in the study will have a clinic visit at the start of the study. To be in the study you have to be on the new smaller Kaletra tablets. If you have been taking the bigger Kaletra tablets, we will ask you to change to the smaller size tablet. This means that you will have to take more tablets but smaller ones. If you prefer to take the larger Kaletra tablets, you will be able to change back later in the study.

A computer program will then decide whether you keep taking Kaletra tablets twice a day or start taking them once a day. Only the computer will be able to choose the group you will be in.

Then, you will have to come and see your hospital doctor and nurse every 4 weeks for 3 months. After that, your doctor will want to see you at your normal clinic visits. It is very important that you take your tablets everyday without forgetting. If you forget to take your medicines, we would like you to tell your doctor or nurse as soon as possible.

6) What happens at blood sampling visits?

At the beginning of the study, we will ask you to come into hospital for a whole day. The nurse will put some cream on your skin to make the skin numb and you will have your first blood test with a thin tube (called a cannula) that will stay in your vein during the whole day. All blood samples will be taken from the cannula, so you should only have one needle prick.

The doctor or the nurse will take your blood 8 times during the day to test the level of Kaletra just before and just after you take your medicines and at times in between.

If the computer decides that you should take Kaletra tablets once a day, we will ask you to come back to the hospital for a second full day of blood sampling 4 weeks later. You may need to stay overnight.

You will not need to come back to the hospital for a whole day if the computer decides that you continue to take your medicine twice a day.

7) What else do I need to know?

We also want to know how you feel about taking your medicines. During the study we will ask you and your family to answer some questions at the clinic visits. These won’t take long and are just about how you feel taking this medicine.
8) Cons to taking part?

- If you change treatment from twice-daily to once-daily Kaletra there is a small risk that the amount of virus in your blood will increase. This can also happen if you forget to take your medicines everyday. If this is the case, the virus will have a higher chance of becoming stronger and the medicine will not work as well. If this happens, your doctor may want you to take Kaletra twice a day like before. We will also ask you to come to the clinic for an extra visit and we will do a blood test to check that the virus level is low.

- If you are taking Kaletra once daily, you will need to take more tablets in one go but only once a day.

- If you change to taking Kaletra once daily, you may need to stay overnight or come back for a blood sample the next morning before you take your medicines.

- If you take Kaletra once a day, there is also a small chance you could get an upset stomach and diarrhoea. This generally only lasts a few days before you feel better again. Not everyone gets side effects from medicines. Some people don't get any at all. If you have any side effects, your doctor can give you some other medicine to take with the anti-HIV medicines that will stop or reduce side effects from happening.

9) Is the information in the study kept private?

- **All information collected during KONCERT will be kept completely private.** This means that we will use a number and your date of birth instead of your name.
- We will tell your GP that you are taking part of the study, but only if you and your parents are ok about it.

10) What happens at the end of KONCERT?

At the end of the study, you will continue to take the same treatment as normal unless your clinic doctor tells you to change. You and your doctor will continue to make decisions about you medicines once the study has finished.

**Thank you for taking the time to consider this study. Please ask any questions if there are things you don’t understand and let us know what you think.**
We would like to invite you to take part in our research study. Before you decide, read this information sheet and ask your parents and your doctor or nurse if there is something you don’t understand.

1) What is a research study?

A research study tests how well new medicines and other treatments work and are safe to use in people. A group of researchers (including your clinic doctor and research nurse) need to collect information about the medicine you are taking. This will help to improve health and care for children and young people living with HIV who need to take the same medicine. This study is called KONCERT.

2) What is the KONCERT research study?

KONCERT is organised by a European group called PENTA. KONCERT is a study for children who are doing really well on their anti-HIV medicines. Children from many European countries will take part in this study.

As you know, it is very important to take your anti-HIV medicines every day but sometimes it can be difficult to take them several times a day. If medicines can be given once a day without any problems, this may make them easier to take. We would like to know if it is safe to take Kaletra once a day instead of twice a day in children.

3) Why have I been chosen?

You have been chosen to take part in KONCERT because you are taking Kaletra everyday and because your virus is undetectable (asleep) and your CD4 count (fighter cells) is good. We are going to ask 160 children just like you from all across Europe to be involved.

4) Do I have to take part?

No. It is up to you and your parents whether or not you take part in this study and it is OK if you do not want to take part.

If you decide to take part, **you can stop the study at any time without giving a reason** and your doctor will still look after you as normal. If you do stop, we would like to know why so we can make the next study better.
5) What happens in the study?

All children in the study will have a clinic visit at the start of the study. If you have been taking the bigger Kaletra tablet, we will ask you to change to the smaller size tablet. This means that you will have to take more tablets but smaller ones. If you prefer to take the larger Kaletra tablets, you will be able to change back later in the study.

A computer program will then decide whether you keep taking Kaletra tablet twice a day or start taking it once a day. Only the computer will be able to choose the group you will be in.

Then, you will have to come and see your hospital doctor and nurse every 4 weeks for 3 months. After 3 months, your doctor will want to see you every 12 weeks to check how well you are doing until the study ends. It is very important that you take your tablets everyday without forgetting. If you forget to take your medicines, we would like you to tell your doctor or nurse as soon as possible.

6) What else do I need to know?

We also want to know how you feel about taking your medicines. During the study we will ask you and your family to answer some questions at the clinic visits. These won’t take long and are just about how you feel taking this medicine.

7) Cons to taking part?

- If you have changed treatment from twice-daily to once-daily Kaletra there is a small risk that the amount of virus in your blood will increase. This can also happen if you forget to take your medicines everyday. If this is the case, the virus will have a higher chance of becoming stronger and the medicine will not work as well. If this happens, your doctor may want you to take Kaletra twice a day like before. We will also ask you to come to the clinic for an extra visit and we will do a blood test to check that the virus level is low.

- If you are taking Kaletra once daily, you will need to take more tablets in one go but only once a day.

- If you take once a day, there is also a small chance you could get an upset stomach and diarrhoea. This generally only lasts a few days before you feel better again. Not everyone gets side effects from medicines. Some people don’t get any at all. If you have any side effects, your doctor can give you some other medicine to take with the anti-HIV medicines that will stop or reduce side effects from happening.
8) Is the information in the study kept private?

- All information collected during KONCERT will be kept completely private. This means that we will use a number and your date of birth instead of your name.
- We will tell your GP that you are taking part of the study, but only if you and your parents are ok about it,

9) What happens at the end of KONCERT?

At the end of the study, you will continue to take the same treatment as normal unless your clinic doctor tells you to change. Your doctor will continue to make decisions about you medicines once the study has finished.

Thank you for taking the time to consider this study. Please ask any questions if there are things you don’t understand and let us know what you think.
APPENDIX 2: SAMPLE CONSENT FORMS
1. Consent form for KONCERT and PK study – to be printed on headed paper

KONCERT AND BLOOD SAMPLING DAYS
CONSENT FORM FOR PARENTS

Please write your initials in each box if you agree:

I have read and understood the information sheet on KONCERT. I understand the benefits and disadvantages of my child participating in this study. The details of this study have been explained to me by Dr………………………… and my questions have been answered satisfactorily.

I agree that my child can take part in this study which is assessing whether Kaletra can be taken once-daily.

I agree that my child can take part in the blood sampling (pharmacokinetic) study.

I know that my child can be withdrawn from the study at any time without it affecting his/her care.

I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.

I agree to my child’s routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth)

I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV and effective treatment

I agree to inform the study doctor if my child starts any new medicines during the period of the study.

I agree to study data including my child’s study number and age being transferred to Abbott, the manufacturer of Kaletra, and to drug agencies in other countries so that they can consider whether once daily Kaletra can be taken safely.

Name of child:________________________________________________________

Name of Parent/Guardian:___________________________________________

Signature of Parent/Guardian:________________________________________ Date:____________

Name of paediatrician:______________________________________________

Signature of paediatrician:___________________________________________ Date:____________

I would/would not like my child’s GP to be notified about participation in this study.

Signature of Parent/Guardian:________________________________________ Date:____________

Name of GP:________________________________________________________

Contact address of GP:______________________________________________
KONCERT CONSENT FORM FOR PARENTS

Please write your initials in each box if you agree:

I have read and understood the information sheet on KONCERT. I understand the benefits and disadvantages of my child participating in this study. The details of this study have been explained to me by Dr.………………………… and my questions have been answered satisfactorily.

☐ I agree that my child can take part in this study which is assessing whether Kaletra can be taken once-daily.

☐ I know that my child can be withdrawn from the study at any time without it affecting his/her care.

☐ I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.

☐ I agree to my child’s routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth)

☐ I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV and effective treatment

☐ I agree to inform the study doctor if my child starts any new medicines during the period of the study.

☐ I agree to study data including my child’s study number and age being transferred to Abbott, the manufacturer of Kaletra, and to drug agencies in other countries so that they can consider whether once daily Kaletra can be taken safely.

Name of child:______________________________________________

Name of Parent/Guardian:____________________________________

Signature of Parent/Guardian:______________________________Date:_____________

Name of paediatrician:_______________________________________

Signature of paediatrician:______________________________Date:____________

I would/would not like my child’s GP to be notified about participation in this study.

Signature of Parent/Guardian:______________________________Date:____________

Name of GP:______________________________________________

Contact address of GP________________________________________

Protocol Version 1. 7 23rd April 2013
3. Consent form for KONCERT and PK study for Participants— to be printed on headed paper

KONCERT AND BLOOD SAMPLING DAYS
CONSENT FORM FOR PARTICIPANTS

Please write your initials in each box if you agree:

I have read and understood the information sheet on KONCERT. I understand the benefits and disadvantages of participating in this study. The details of this study have been explained to me by Dr.________________________ and my questions have been answered satisfactorily.

☐ I agree to take part in this study which is assessing whether Kaletra can be taken once-daily.

☐ I agree to take part in the blood sampling (pharmacokinetic) study.

☐ I know that I can withdraw from the study at any time without it affecting my care.

☐ I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.

☐ I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth)

☐ I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV and effective treatment

☐ I agree to inform the study doctor if I start any new medicines during the period of the study.

☐ I agree to study data including my study number and age being transferred to Abbott, the manufacturer of Kaletra, and to drug agencies in other countries so that they can consider whether once daily Kaletra can be taken safely.

Name of Participant: __________________________________________

Signature of Participant: __________________________ Date: __________

Name of paediatrician: __________________________________________

Signature of paediatrician: __________________________ Date: __________

I would/would not like my GP to be notified about my participation in this study.

Signature of Participant: __________________________ Date: __________

Name of GP: __________________________________________

Contact address of GP__________________________________________________________
4. Consent form for KONCERT for Participants, non PK study – to be printed on headed paper

KONCERT CONSENT FORM FOR PARTICIPANTS

Please write your initials in each box if you agree:

I have read and understood the information sheet on KONCERT. I understand the benefits and disadvantages of participating in this study. The details of this study have been explained to me by Dr………………………… and my questions have been answered satisfactorily.

I agree to take part in this study which is assessing whether Kaletra can be taken once-daily.

I know that I can withdraw from the study at any time without it affecting his/her care.

I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.

I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth)

I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV and effective treatment

I agree to inform the study doctor if I start any new medicines during the period of the study.

I agree to study data including my study number and age being transferred to Abbott, the manufacturer of Kaletra, and to drug agencies in other countries so that they can consider whether once daily Kaletra can be taken safely.

Name of Participant:______________________________

Name of paediatrician:______________________________

Signature of paediatrician:________________________Date:___________

I would/would not like my GP to be notified about my participation in this study.

Signature of Participant:________________________Date:___________

Name of GP:___________________________________

Contact address of GP__________________________________________
APPENDIX 3: SAMPLE ASSENT FORM

1. Assent form for KONCERT and blood sampling study – to be printed on headed paper

KONCERT ASSENT FORM FOR CHILDREN

Title of Study: KONCERT. A study of the level of medicine in the blood (pharmacokinetics), safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir (Kaletra) tablets as part of combination antiretroviral therapy in HIV-1 infected children.

Please tick yes or no to the questions below

1. Have you read (or has someone read to you) the information about this study?   YES □ NO □

2. Do you understand what the study is about or has somebody explained it to you? YES □ NO □

3. Have you asked all the questions you want?........................................................ YES □ NO □

4. Have your questions been answered in a way you understand?.........................YES □ NO □

5. Do you understand how the study might help you?......................................... YES □ NO □

6. Do you understand the risks and benefits of taking part in the study?..............YES □ NO □

7. Do you understand that you are free to stop the study at any time?....................YES □ NO □

8. Do you understand that, if you take part in the study, only a computer will decide whether or not you may be in the group that takes all the Kaletra tablets in one go or twice a day?......................................................................................................YES □ NO □

9. Do you understand that you will need to come to the hospital for a whole day to check the level of drug in your blood?.................................................................YES □ NO □

10. Do you also understand that if you take all your Kaletra tablets in one go, each day during the study, you will need to come back to the hospital for a second full day and check the level of drug in your blood (and maybe sleep there)?............YES □ NO □

11. Do you agree that your blood samples (without your name on) can be used during the study and stored for studies which will help us understand more about your HIV infection? ..................................................................................................YES □ NO □

12. Are you happy to take part?................................................................................YES □ NO □

If any answers are ‘no’ or you don’t want to take part, don’t sign your name.

If you do want to take part, you can sign your name below.

Your name: ___________________________________ Date: ______________

The doctor who explained the study to you needs to sign too:

Doctor’s name (print): __________________________

Signature of doctor: __________________________ Date: ______________

Thank you for your help.
2. Assent form for KONCERT, non blood sampling study – to be printed on headed paper

KONCERT ASSENT FORM FOR CHILDREN

Title of Study: KONCERT. A study of the level of medicine in the blood (pharmacokinetics), safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir (Kaletra) tablets as part of combination antiretroviral therapy in HIV-1 infected children.

Please tick yes or no to the questions below

1. Have you read (or has someone read to you) the information about this study?..... YES NO

2. Do you understand what the study is about or has somebody explained it to you? YES NO

3. Have you asked all the questions you want?................................. YES NO

4. Have your questions been answered in a way you understand?.................. YES NO

5. Do you understand how the study might help you?............................ YES NO

6. Do you understand the risks and benefits of taking part in the study?......... YES NO

7. Do you understand that you are free to stop the study at any time?.......... YES NO

8. Do you understand that, if you take part in the study, only a computer will decide whether or not you may be in the group that takes all the Kaletra tablets in one go or twice a day?................................................................. YES NO

9. Do you agree that your blood samples (without your name on) can be used during the study and stored for studies which will help us understand more about your HIV infection? .......................................................... YES NO

10. Are you happy to take part?.............................................................. YES NO

If any answers are ‘no’ or you don’t want to take part, don’t sign your name.

If you do want to take part, you can sign your name below.

Your name: ___________________________________________

Date: ________________________________

The doctor who explained the study to you needs to sign too:

Doctor’s name (print): ______________________________

Signature of doctor: ________________________________

Date: ________________________________

Thank you for your help.
APPENDIX 4: SAMPLE GP LETTER

To be sent on local headed paper. Sections in italics should be deleted if not applicable.

KONCERT

Dear Dr

The parents of _______ and _______ , him/herself, have agreed to participate in KONCERT. This is a randomised multicentre international trial by PENTA, which is funded by the European Commission (see www.PENTAtrials.org).

KONCERT aims to evaluate whether once-daily dosing of lopinavir/ritonavir is comparable to twice-daily dosing in terms of virological suppression at 48 weeks. Adherence and acceptability will also be compared.

The trial will enrol 160 children under 18 years of age from clinical centres involved in the PENTA network. All children will be followed for at least 48 weeks.

The first children enrolled in each weight band will also participate in a pharmacokinetic study which aims to evaluate the pharmacokinetics of twice-daily lopinavir/ritonavir half strength formulation tablets dosed on body weight, and compare to historical adult and paediatric data of pharmacokinetics of lopinavir/ritonavir soft gel capsules and oral solution respectively to compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children.

Your patient ___________________________ has been randomised to take Lopinavir/ritonavir tablets once-daily /continue on twice-daily tablets. He/she is /is not participating in the pharmacokinetic study.

I would be very grateful if you could inform me of any concomitant medication that you may plan to prescribe to this patient during the study.

I enclose a summary of the trial and a copy of the Patient Information Sheet. If you would like a copy of the full protocol or have any comments or problems, please contact:

Dr ______________________

Enc.
Trial Summary
Patient Information Sheet
Medication not permitted/precautions
APPENDIX 5: ADHERENCE QUESTIONNAIRES

I  Adherence questionnaire for carers
II  Adherence questionnaire for young people
KONCERT: ADHERENCE QUESTIONNAIRE FOR CARERS

To the doctor or nurse: please complete the following details and write the names, colour and type (e.g. pink liquid) of medicines that the child has been taking in the tables in question 3 and 8. If the carer is short of time, please ask them to complete questions 6, 7, 8 and 9 in particular.

To be completed by the doctor or nurse:

<table>
<thead>
<tr>
<th>Date of Birth:</th>
<th>KONCERT Trial Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous code:</td>
<td>Date of Assessment:</td>
</tr>
</tbody>
</table>

Week no. (please ring):
-2  0  4  12  24
48  72  96

Completed by carer alone?
Yes ☐ No ☐
If no, who else was involved?

If not completed:
Not enough time ☐ Refusal ☐
DNA ☐ Parent/carer not available ☐
Other ☐ specify:

To the carer: We know that it can be difficult giving medicines to children everyday. We are interested in finding out what it is like for you and your family. Please tick the answer that best describes what is happening and how you feel at the moment. Being honest about the good and bad things about these medicines may help others in the future. Please only think about the antiretroviral medicines your child is taking, not any other drugs. Thank you.

1) What is your relationship to the child? Mother ☐ Father ☐
Other ☐ (please specify) ____________________

2) Who else gives antiretroviral medicines to your child? ______________________

3) At what times does your child usually take their antiretroviral medicines?
(e.g. breakfast, lunch, after nursery, evening)

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Colour, Type</th>
<th>Time of 1st dose</th>
<th>Time of 2nd dose (if 2nd dose given)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
</tbody>
</table>

4) Which dose, if any, is the most difficult overall for you/your child?
morning ☐ lunchtime/after school ☐ evening ☐
none are difficult ☐ all are difficult ☐

5) What helps you give the medicines? (tick all that apply)
Labels ☐ Medicine Chart ☐ Pill box ☐
MEM Caps ☐ Text messages ☐ Timer/alarm clock/beeper ☐
Diary ☐ Daily events (e.g. breakfast time) ☐
Other ☐ Name them: ________________________________

6) How much does giving antiretroviral medicines to your child interfere with you/your child’s everyday life?
a lot ☐ quite a lot ☐ not much ☐ not at all ☐
How? ___________________________________________
7) When was the last time your child missed any antiretroviral medicines? (tick box):
Within the last week □ 1-2 weeks ago □ 2-4 weeks ago □
1-3 months ago □ Missed nothing in the last 3 months □

8) Can you say how many times your child has missed a dose of their antiretroviral medicines over the last 3 days?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Yesterday</th>
<th>Day before yesterday</th>
<th>3 days ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>2.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>3.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>4.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
</tbody>
</table>

9) Please mark on the line below the amount of medicines your child has taken since the last clinic visit. 0% means no medicines taken since the last clinic visit, 50% means about half the medicines were taken, 100% means not missed any doses of any of the medicines. We would be surprised if it was 100% for most children.

10) If your child has missed any doses since your last visit to the clinic, please tick the reason(s) and say which medicine(s): No doses missed since last visit to the clinic □

<table>
<thead>
<tr>
<th>Because:</th>
<th>Name of medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>You had run out of medicine?</td>
<td>□</td>
</tr>
<tr>
<td>Your child has problems taking some of the medicine?</td>
<td>□</td>
</tr>
<tr>
<td>You had forgotten?</td>
<td>□</td>
</tr>
<tr>
<td>You think the medicines are toxic or harmful?</td>
<td>□</td>
</tr>
<tr>
<td>Taking the medicine is difficult with school hours, meals, sleep etc</td>
<td>□</td>
</tr>
<tr>
<td>Your child refused to take them</td>
<td>□</td>
</tr>
<tr>
<td>Your child was being looked after by someone else?</td>
<td>□</td>
</tr>
<tr>
<td>You did not want other people to know your child was taking medicine?</td>
<td>□</td>
</tr>
<tr>
<td>Your child was unwell?</td>
<td>□</td>
</tr>
<tr>
<td>Your routine, or your child’s routine, was different from normal (e.g. holidays, weekends etc)?</td>
<td>□</td>
</tr>
<tr>
<td>You were too depressed or unwell?</td>
<td>□</td>
</tr>
<tr>
<td>You are fed up giving medicine?</td>
<td>□</td>
</tr>
</tbody>
</table>

Further details or any other reason (please name them): __________________________

Thank you for taking the time to fill out this form; please add any comments you have on the back.
KONCERT:
ADHERENCE QUESTIONNAIRE FOR YOUNG PEOPLE

To the doctor or nurse: please complete the following details and write the names, colour and type (eg blue pill, pink liquid) of the medicines that the child/teenager has been taking in the tables in question 1 and 7. If the child/teenager is short of time, please ask them to complete questions 5, 6,7, 8 and 9 in particular.

To be completed by the doctor or nurse:

Date of Birth: 
KONCERT Trial Number: 
Anonymous code: 
Date of Assessment: 

Week no. (please ring): 
-2 0 4 12 24 
48 72 96 
Completed by child/young person alone? 
Yes □ No □ 
If no, who else was involved? 

If not completed: 
Not enough time □ Refusal □ 
DNA □ Other □ specify: 

To the child or teenager: We know that it can be difficult taking antiretroviral medicines everyday. We are interested in finding out what it is like for you and your family. Please tick the answer that best describes what is happening and how you feel at the moment. Being honest about the good and bad things about these medicines may help others in the future. Please only think about the antiretroviral medicines your are taking, not any other drugs. Thank you.

1) At what time do you usually take your antiretroviral medicines? (eg breakfast, lunch, after school, evening)

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Colour, Type</th>
<th>Time of 1st dose</th>
<th>Time of 2nd dose (if 2nd dose given)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>1st dose</td>
<td>2nd dose</td>
</tr>
</tbody>
</table>

2) Which dose, if any, is the most difficult for you? 
morning □ lunchtime/after school □ evening □ 
none are difficult □ all are difficult □

3) Does any one remind you when to take your medicine? Yes □ No □ 
If someone reminds you, who is it? 

4) What helps you take the medicines? (tick all that apply) 
Labels □ Medicine Chart □ Pill box □ 
MEM Caps □ Text messages □ Timer/alarm clock/beeper □ 
Diary □ Daily events (eg breakfast time) □ 
Support from Mum/Dad/Carer □ Knowing my blood results □ 
Knowing why I need to take medicines □ 
Other □ Name them: 

Protocol Version 1. 7 23rd April 2013
5) How much does taking antiretroviral medicines interfere with your everyday life?

- a lot □
- quite a lot □
- not much □
- not at all □

How? ____________________________________________ ________________

6) When was the last time you missed any of your antiretroviral medicines? (tick box):

- Within the last week □
- 1- 2 weeks ago □
- 2- 4 weeks ago □
- 1- 3 months ago □
- Missed nothing in the last 3 months □

7) Can you say how many times your child has missed a dose of your antiretroviral medicines over the last 3 days?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Yesterday</th>
<th>Day before yesterday</th>
<th>3 days ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>2.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>3.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
<tr>
<td>4.</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
<td>..... dose(s) missed</td>
</tr>
</tbody>
</table>

8) Please mark on the line below the amount of medicines you have taken since the last clinic visit. 0% means no medicines taken since the last clinic visit, 50% means about half the medicines were taken, 100% means not missed any doses of any of the medicines. We would be surprised if it was 100% for anyone.

0 10% 20% 30% 40% 50% 60% 70% 80% 90% 100

9) If you have missed any doses since your last visit to the clinic, please tick the reason(s) why and say which medicine(s):

No doses missed since last visit to the clinic □

Because:

- You had run out of medicine? □
- You had forgotten? □
- You think the medicine is toxic or harmful? □
- Taking medicine is difficult with school hours, meals, sleep etc □
- You didn’t want to take it? □
- You did not want other people to know you were taking medicine? □
- You were unwell? □
- Your routine was different from normal (eg holidays, weekends etc)? □
- You are fed up taking medicine? □

Further details or any other reason (please name them) : ________________________________________

Thank you for taking the time to fill out this form; please add any comments you have:
APPENDIX 6: ACCEPTABILITY QUESTIONNAIRES

I. Carers – Week 0
II. Carers – End of trial/switch back to twice daily
III. Young Person – Week 0
IV. Young people - End of Trial/Switch back to twice daily
### KONCERT ACCEPTABILITY QUESTIONNAIRES FOR CARERS
#### WEEK 0

<table>
<thead>
<tr>
<th>Date of Birth:</th>
<th>KONCERT Trial Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous code:</td>
<td>Date of Assessment:</td>
</tr>
</tbody>
</table>

**Completed by carer alone?**
- Yes □
- No □

**If no, who else was involved?**
________________________________________

**If not completed:**
- Not enough time □
- Refusal □
- DNA □
- Parent/carer not available □
- Other □

**Specify:**
________________________________________

---

**You have agreed for your child to be enrolled in KONCERT. This study will compare taking Kaletra tablets twice-daily and once-daily.**

**Before you know whether your child will be switching from twice-daily to once-daily Kaletra we would like to find out what you feel the benefits for you and your child could be of switching to once-daily dosing. We will repeat this questionnaire at the end of the study (week 48) or if your child stops taking once-daily tablets and switches back to twice-daily, to see if your views have changed.**

1) **What is your relationship to the child?**
   - Mother □
   - Father □
   - Other (please specify) ____________________

2) **Who gives medicines to the child?**
   ____________________

3) **Is your child taking:**
   - Kaletra full strength 200/50 mg tablets (adult size) only □
   - Kaletra half strength 100/25 mg tablets (child size) only □
   - A mixture of Kaletra adult and child size tablets □

4) **Which size do you find easier to give?**
   - Adult size tablets □
   - Child size tablets □
   - No difference □

   **Comment:**
   ____________________________________________

5) **How do you think switching from twice-daily to once-daily Kaletra tablets will make things for you?**
   - A lot easier □
   - A little easier □
   - No difference □
   - A little more difficult □
   - A lot more difficult □

   **Please give reasons:**
   ____________________________________________

   ____________________________________________
6) **How do you think switching from twice-daily to once-daily Kaletra tablets will make things for your child?**

A lot easier ☐  A little easier ☐  No difference ☐
A little more difficult ☐  A lot more difficult ☐

**Please give reasons:**

<table>
<thead>
<tr>
<th>Reason</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7) **Do you think it will be easier to give the tablets if they are once-daily?**

Yes ☐  No ☐  Unsure ☐

8) **What time do you think will be best to give your child his/her medicines***?

Morning ☐  Afternoon ☐  Evening ☐

*Your child may have to take them in the morning until both blood sampling days have been completed, then you can choose*

9) **Have any of the following been a problem in the past:**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Frequently ☐</th>
<th>Sometimes ☐</th>
<th>Rarely ☐</th>
<th>Never ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remembering to take medicines</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td><strong>Number of tablets</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td><strong>Size of tablets</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td><strong>Taste of tablets</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Thank for completing this questionnaire.**
**KONCERT ACCEPTABILITY QUESTIONNAIRES – CARERS END OF STUDY OR SWITCH BACK TO TWICE-DAILY**

**Date of Birth:**

**Anonymous code:**

**Completed by carer alone?**

Yes ☐ No ☐

**If no, who else was involved?**

**If not completed:**

- Not enough time ☐
- Refusal ☐
- DNA ☐
- Parent/carer not available ☐
- Other ☐ specify:

**KONCERT Trial Number:**

**Currently on:**

- QD Kaletra ☐
- BID Kaletra ☐

**Date of Assessment:**

**Date of restart of BID:**

<table>
<thead>
<tr>
<th>Morning</th>
<th>Afternoon</th>
<th>Evening</th>
</tr>
</thead>
</table>

---

Thank you for enrolling your child in KONCERT. This study was comparing taking Kaletra tablets twice-daily and once-daily.

Now that the study has finished or your child has changed back to twice-daily dosing of Kaletra we would like to get some information from you about what you feel the benefits or drawbacks have been for you and your child.

1) **What is your relationship to the child?**

- Mother ☐
- Father ☐
- Other (please specify) _____________

2) **How did switching from twice-daily to once-daily tablets make things for you?**

- A lot easier ☐
- A little easier ☐
- No difference ☐
- A little more difficult ☐
- A lot more difficult ☐

Please give reasons:

3) **How did switching from twice-daily to once-daily tablets make things for your child?**

- A lot easier ☐
- A little easier ☐
- No difference ☐
- A little more difficult ☐
- A lot more difficult ☐

Please give reasons:

4) **Do you think it was easier to give the tablets once-daily?**

- Yes ☐
- No ☐
- Unsure ☐

5) **What time did you give your child his/her once-daily tablets?**

- Morning ☐
- Afternoon ☐
- Evening ☐
6) **Were any of these issues a problem with taking tablets once-daily?**

<table>
<thead>
<tr>
<th></th>
<th>Frequently ☐</th>
<th>Sometimes ☐</th>
<th>Rarely ☐</th>
<th>Never ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remembering to take medicines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of tablets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size of tablets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Taste of tablets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Please specify: ____________________________

---

Thank you for your help.
KONCERT ACCEPTABILITY QUESTIONNAIRES FOR YOUNG PEOPLE
WEEK 0

Date of Birth: ____________________________
Anonymous code: ____________________________
Completed by young person alone?
Yes ☐ No ☐
If no, who else was involved? ____________________________
Date of Assessment: ____________________________
KONCERT Trial Number: ____________________________

If not completed:
Not enough time ☐
Refusal ☐
DNA ☐
Other ☐ specify: ____________________________

Is he/she currently taking?
Half strength Kaletra tablets (100/25mg) ☐
Full strength Kaletra tablets (200/50mg) ☐
Combination of above ☐

Thank you for agreeing to be enrolled in KONCERT. This study will compare taking Kaletra tablets twice-daily and once-daily.
Before you know whether you will be switching from twice-daily to once-daily Kaletra we would like to find out what you feel the benefits could be of switching to once-daily dosing. We will repeat this questionnaire at the end of the study (week 48) or if you decide to stop taking once-daily tablets and switch back to twice-daily, to see if your views have changed.

1) Are you taking:
Kaletra full strength 200/50 mg tablets (adult size) only ☐
Kaletra half strength 100/25 mg tablets (child size) only ☐
A mixture of Kaletra adult and child size tablets ☐

2) Which size do you find easier to take?
Adult size tablets ☐ Child size tablets ☐ No difference ☐

Comment: __________________________________________________________

3) How do you think switching from twice-daily to once-daily Kaletra tablets will make things for you?
A lot easier ☐ A little easier ☐ No difference ☐
A little more difficult ☐ A lot more difficult ☐

Please give reasons:
________________________________________________________
________________________________________________________

4) Do you think it will be easier to take the tablets if they are once-daily?
Yes ☐ No ☐ Unsure ☐

5) What time would you prefer to take your medicines*?
Morning ☐ Afternoon ☐ Evening ☐

*You may have to take them in the morning until you have done both blood sampling days, then you can choose
6) **Have any of the following been a problem in the past:**

<table>
<thead>
<tr>
<th><strong>Remembering to take medicines</strong></th>
<th>Frequently</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of tablets</strong></td>
<td>Frequently</td>
<td>Sometimes</td>
<td>Rarely</td>
<td>Never</td>
</tr>
<tr>
<td><strong>Size of tablets</strong></td>
<td>Frequently</td>
<td>Sometimes</td>
<td>Rarely</td>
<td>Never</td>
</tr>
<tr>
<td><strong>Taste of tablets</strong></td>
<td>Frequently</td>
<td>Sometimes</td>
<td>Rarely</td>
<td>Never</td>
</tr>
</tbody>
</table>

Thank for completing this questionnaire.
KONCERT ACCEPTABILITY QUESTIONNAIRES – YOUNG PEOPLE
END OF STUDY or SWITCH BACK TO TWICE-DAILY

To be completed by nurse/doctor:

<table>
<thead>
<tr>
<th>Date of Birth:</th>
<th>Anonymous code:</th>
<th>Date of Assessment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>KONCERT Trial Number:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Completed by young person alone? 
Yes ☐ No ☐

If no, who else was involved? ________________

If not completed: 
Not enough time ☐
Refusal ☐
DNA ☐
Other ☐ specify: ________________

Currently on: 
Once-daily Kaletra ☐
Twice-daily Kaletra ☐

Date of restart of BID: ___ / ___ / ___

Thank you for taking part in KONCERT. This study was comparing taking Kaletra tablets twice-daily and once-daily

Now that the study has finished or you changed back to twice-daily dosing of Kaletra, we would like to get some information from you about what you feel the benefits or drawbacks have been.

1) How did switching from twice-daily to once-daily tablets make things for you?

A lot easier ☐ A little easier ☐ No difference ☐
A little more difficult ☐ A lot more difficult ☐

Please give reasons: ________________________________

2) Do you think it was easier to take the tablets once-daily?

Yes ☐ No ☐ Unsure ☐

3) What time did you take your once-daily tablets?

Morning ☐ Afternoon ☐ Evening ☐

4) Were any of these issues a problem with taking tablets once-daily?

<table>
<thead>
<tr>
<th>Remembering to take medicines</th>
<th>Frequently ☐ Sometimes ☐ Rarely ☐ Never ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tablets</td>
<td>Frequently ☐ Sometimes ☐ Rarely ☐ Never ☐</td>
</tr>
<tr>
<td>Size of tablets</td>
<td>Frequently ☐ Sometimes ☐ Rarely ☐ Never ☐</td>
</tr>
<tr>
<td>Taste of tablets</td>
<td>Frequently ☐ Sometimes ☐ Rarely ☐ Never ☐</td>
</tr>
</tbody>
</table>

Please specify: ________________________________

Thank you for completing this questionnaire.
APPENDIX 7: PRE-PK INFORMATION SHEET

To be given to families with children participating in the PK study at screening (for week 0 PK day) and at week 0 (for week 4 PK day – OD arm only). Please add the required information first and ask the families to bring the completed sheet back to clinic on the PK day.

KONCERT information for week 0 blood sampling day

<table>
<thead>
<tr>
<th>KONCERT trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weekday and date of blood sampling day</th>
</tr>
</thead>
<tbody>
<tr>
<td>____________________________, __ / __ / __</td>
</tr>
</tbody>
</table>

Thank you and your child for participating in KONCERT and taking part in the blood sampling days. We will be looking at the level of Kaletra in your child’s blood during the course of the day. It is therefore important that we get accurate information so that we can interpret this properly. Please keep the empty bottles of Kaletra tablets from this visit.

**Over the next 4 weeks**
Your child should take every dose of Kaletra tablets between now and the blood sampling day as prescribed by your doctor.

**The day before the blood sampling day (________________, ________________)**
It is important that the dose this evening is taken around 12 hours before you get to clinic tomorrow.

The evening before the blood sampling day we recommend that you give _____ half strength Kaletra tablets (100/25mg) at ___:___ pm.

Please record the actual number of tablets taken _____ and the time they were taken ___ : ___

Also the time of the last meal ___ : ___ pm

**On the day of the blood sampling (________________, ________________)**
Please – no breakfast and no morning dose of any medication for your child (we will provide breakfast at the hospital once the first blood has been taken)
You should try to arrive at the hospital at ____ : ____ am.
Please bring back all the bottles of Kaletra tablets (even if empty) that you were given at the last clinic visit.

If you have any questions or problems, please ring:
_________________________ on ________________________________
KONCERT information for week 4 blood sampling day

<table>
<thead>
<tr>
<th>KONCERT trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekday and date of blood sampling day</td>
</tr>
</tbody>
</table>

Thank you and your child for participating in KONCERT and taking part in the blood sampling days. We will be looking at the level of Kaletra in your child’s blood during the course of the day. It is therefore important that we get accurate information so that we can interpret this properly. Please keep the empty bottles of Kaletra tablets from this visit.

Over the next 4 weeks
Your child should take every dose of Kaletra tablets between now and the blood sampling day in the morning, as prescribed by your doctor.

The day before the blood sampling day (_______________, ________________)
It is important that the dose this morning is taken around 24 hours before you get to clinic tomorrow.

The morning before the blood sampling day we recommend that you give ____ half strength Kaletra tablets (100/25mg) at ___:___ am.

Please record the actual number of tablets taken ____ and the time they were taken ___ : ___

Also the time of the last meal ___ : ___ am

On the day of the blood sampling (_______________, ________________)
Please – no breakfast and no morning dose of any medication for your child (we will provide breakfast at the hospital once the first blood has been taken)
You should try to arrive at the hospital at ____ : ____ am.
Please bring back all the bottles of Kaletra tablets (even if empty) that you were given at the last clinic visit.

If you have any questions or problems, please ring:
__________________________ on __________________________
APPENDIX 8: CDC CLASSIFICATIONS
CDC 1994 REVISED CLASSIFICATION SYSTEM FOR HIV-INFECTION IN CHILDREN (MMWR 1994; 43 [RR-12]:1-10)

Clinical Categories for Children with Human Immunodeficiency Virus (HIV) Infection

CATEGORY N: NOT SYMPTOMATIC
Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

CATEGORY A: MILDLY SYMPTOMATIC
Children with two or more of the conditions listed below but none of the conditions listed in Categories B and C.

- Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC
Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to:

- Anaemia (< 8 g/dL), neutropaenia (< 1.0 x 10^9/l), or thrombocytopaenia (<100 x 10^9/l) persisting > 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (> 2 months) in children > 6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhoea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or oesophagitis with onset before 1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leimyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting > 1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)
CATEGORY C: SEVERELY SYMPTOMATIC*

Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types:

- Septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings):
  a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests;
  b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age);
  c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathological reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or oesophagitis for any duration affecting a child > 1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunological phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Pneumocystis jiroveci pneumonia (formerly carinii)
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicaemia, recurrent
- Toxoplasmosis of the brain with onset at > 1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings:
  a) persistent weight loss > 10% of baseline OR
  b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child > 1 year of age OR
  c) < 5th percentile on weight-for-height chart on two consecutive measurements, >30 days apart PLUS a) chronic diarrhoea (i.e., at least two loose stools per day for >30 days) OR b) documented fever (for > 30 days, intermittent or constant)

Definitive diagnosis: microscopy (histology or cytology); culture; antigen detection.
Presumptive diagnosis: characteristic clinical presentation, supported by investigations other than microscopy or culture and after exclusion of other causes in the differential diagnosis.
## APPENDIX 9: UNDESIRABLE EFFECTS OF LOPINAVIR/RITONAVIR

From the Kaletra SPC dated 24/11/2008
Further updates can be found at http://www.emea.europa.eu/humandocs/Humans/EPAR/kaletra/kaletra.htm

### Undesirable effects in clinical studies in adult patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral infection</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon</td>
<td>Skin benign neoplasm, cyst</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Anaemia, leucopenia and lymphadenopathy</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Uncommon</td>
<td>Hypogonadism male, Cushing syndrome, hypothyroidism</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>Uncommon</td>
<td>Avitaminosis, dehydration, oedema, increased appetite, lactic acidosis, obesity, anorexia, diabetes mellitus, hyperglycaemia, hypercholesteremia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Abnormal dreams, agitation, anxiety, confusion, depression, dyskinesia, emotional lability, decreased libido, nervousness, abnormal thinking</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, paresthesia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dizziness, amnesia, ataxia, encephalopathy, facial paralysis, hypertonia, neuropathy, peripheral neuritis, somnolence, tremor, taste loss, taste perversion, migraine, extrapyramidal syndrome</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Abnormal vision, eye disorder</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Palpitation, lung oedema, myocardial infarct</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypertension, thrombophlebitis, vasculitis, varicose vein, deep thrombophlebitis, vascular disorder</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Dyspnoea, rhinitis, cough increased</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Nausea, vomiting, abdominal pain, abnormal stools, dyspepsia, flatulence, gastrointestinal disorder</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Abdomen enlarged, constipation, dry mouth, dysphagia, enterocolitis, eructation, oesophagitis, faecal incontinence, gastritis, gastroenteritis, haemorrhagic colitis, mouth ulcerations, pancreatitis2, sialadenitis, stomatitis, ulcerative stomatitis, periodontitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Cholecystitis, hepatitis, hepatomegaly, liver fatty deposit, liver tenderness</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash, lipodystrophy, acne</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, nail disorder, pruritis, seborrhoea, skin discoloration, skin ulcer, face oedema, sweating, skin striae</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Arthralgia, arthrosis, myalgia, back pain, joint disorder</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Kidney calculus, urine abnormality, albuminuria, hypercalcinuria, nephritis, hyperuricemia</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Abnormal ejaculation, amenorrhoea, breast enlargement, gynecomastia, impotence, menorrhagia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia, pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Chest pain, chest pain substernal, chills, fever, flu syndrome, malaise, peripheral oedema, drug interaction</td>
</tr>
<tr>
<td>Investigations</td>
<td>Very common</td>
<td>Increased triglycerides, increased total cholesterol, increased GGT</td>
</tr>
<tr>
<td></td>
<td>Common (Grade 3/4)</td>
<td>Increased glucose, increased amylase, increased SGOT/AST, increased SGPT/ALT, liver function tests abnormal</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Decreased glucose tolerance, weight gain, weight loss, increased bilirubin, hormone level altered, lab test abnormal</td>
</tr>
</tbody>
</table>

**Paediatric patients**

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Common</th>
<th>Viral infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Taste perversion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Constipation, vomiting, pancreatitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Common</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash, dry skin</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common (Grade 3 or 4)</td>
<td>Increased activated partial thromboplastin time, decreased haemoglobin, decreased platelets, increased sodium, increased potassium, increased calcium, increased bilirubin, increased SGPT/ALT, increased SGOT/AST, increased total cholesterol, increased amylase, increased uric acid, decreased sodium, decreased potassium, decreased calcium, decreased neutrophils</td>
</tr>
</tbody>
</table>
## APPENDIX 10: TOXICITY GRADINGS
(Adapted from National Institute of Health (Division of AIDS USA) toxicity table for grading severity of adult and paediatric adverse events (December, 2004) Clarification August 2009)

### CLINICAL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESTIMATING SEVERITY GRADE</strong></td>
<td><strong>Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table</strong></td>
<td><strong>Symptoms causing no or minimal interference with usual social &amp; functional activities</strong></td>
<td><strong>Symptoms causing greater than minimal interference with usual social &amp; functional activities</strong></td>
<td><strong>Symptoms causing inability to perform usual social &amp; functional activities</strong></td>
</tr>
<tr>
<td><strong>SYSTEMIC</strong></td>
<td>Localized urticaria (wheals) with no medical intervention indicated</td>
<td>Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated</td>
<td>Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm</td>
<td>Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema</td>
</tr>
<tr>
<td>Chills</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
<td>NA</td>
</tr>
<tr>
<td>Fatigue/Malaise</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
<td>Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Fever (nonaxillary)</td>
<td>37.7 – 38.6°C</td>
<td>38.7 – 39.3°C</td>
<td>39.4 – 40.5°C</td>
<td>&gt; 40.5°C</td>
</tr>
<tr>
<td>Pain (indicate body site)</td>
<td>Pain causing no or minimal interference with usual social &amp; functional activities</td>
<td>Pain causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Pain causing inability to perform usual social &amp; functional activities</td>
<td>Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>NA</td>
<td>5 – 9% loss in body weight from baseline</td>
<td>10 – 19% loss in body weight from baseline</td>
<td>≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
</tr>
<tr>
<td>-----------</td>
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<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection (any other than HIV infection)</td>
<td>Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social &amp; functional activities OR Operative intervention (other than simple incision and drainage) indicated</td>
<td>Life-threatening consequences (e.g., septic shock)</td>
</tr>
<tr>
<td><strong>INJECTION SITE REACTIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain (pain without touching) OR Tenderness (pain when area is touched)</td>
<td>Pain/tenderness causing no or minimal limitation of use of limb</td>
<td>Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Pain/tenderness causing inability to perform usual social &amp; functional activities</td>
<td>Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness</td>
</tr>
<tr>
<td>Injection site reaction (localized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adult &gt; 15 years</strong></td>
<td>Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm² – 81 cm²)</td>
<td>Erythema OR Induration OR Edema &gt; 9 cm any diameter (or &gt; 81 cm²)</td>
<td>Uceration OR Secondary infection OR Phlebitis OR sterile abscess OR Drainage</td>
<td>Necrosis (involving dermis and deeper tissue)</td>
</tr>
<tr>
<td><strong>Paediatric ≤ 15 years</strong></td>
<td>Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter</td>
<td>Erythema OR Induration OR Edema &gt; 2.5 cm diameter but &lt; 50% surface area of the extremity segment (e.g., upper arm/thigh)</td>
<td>Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR sterile abscess OR Drainage</td>
<td>Necrosis (involving dermis and deeper tissue)</td>
</tr>
<tr>
<td>Pruritis associated with injection</td>
<td>Itching localized to injection site AND Relieved spontaneously or with &lt; 48 hours treatment</td>
<td>Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment</td>
<td>Generalized itching causing inability to perform usual social &amp; functional activities</td>
<td>NA</td>
</tr>
<tr>
<td><strong>SKIN – DERMATOLOGICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Thinning detectable by study participant (or by caregiver for young children and disabled adults)</td>
<td>Thinning or patchy hair loss detectable by health care provider</td>
<td>Complete hair loss</td>
<td>NA</td>
</tr>
</tbody>
</table>
## CLINICAL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous reaction – rash</td>
<td>Localized macular rash</td>
<td>Diffuse macular, maculopapular, or morbilliform rash OR Target lesions</td>
<td>Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site</td>
<td>Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Slight or localized</td>
<td>Marked or generalized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Slight or localized</td>
<td>Marked or generalized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pruritis (itching – no skin lesions)</td>
<td>Itching causing no or minimal interference with usual social &amp; functional activities</td>
<td>Itching causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Itching causing inability to perform usual social &amp; functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

## CARDIOVASCULAR

<table>
<thead>
<tr>
<th>Cardiac arrhythmia (general) (By ECG or physical exam)</th>
<th>Asymptomatic AND No intervention indicated</th>
<th>Asymptomatic AND Non-urgent medical intervention indicated</th>
<th>Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated</th>
<th>Life-threatening arrhythmia OR Urgent intervention indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac-ischemia/infarction</td>
<td>NA</td>
<td>NA</td>
<td>Symptomatic ischemia (stable angina) OR Testing consistent with ischemia</td>
<td>Unstable angina OR Acute myocardial infarction</td>
</tr>
<tr>
<td>Hemorrhage (significant acute blood loss)</td>
<td>NA</td>
<td>Symptomatic AND No transfusion indicated</td>
<td>Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated</td>
<td>Life-threatening hypotension OR Transfusion of &gt; 2 units packed RBCs (for children &gt; 10 cc/kg) indicated</td>
</tr>
</tbody>
</table>

### Hypertension

<table>
<thead>
<tr>
<th>Adult &gt; 17 years (with repeat testing at same visit)</th>
<th>140-159 mm Hg systolic OR 90-99 mmHg diastolic</th>
<th>160-179 mm Hg systolic OR 100-109 mmHg diastolic</th>
<th>≥ 180 mm Hg systolic OR ≥ 110 mmHg diastolic</th>
<th>Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric ≤ 17 years (with repeat testing at same visit)</td>
<td>NA</td>
<td>91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)</td>
<td>≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)</td>
<td>Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)</td>
</tr>
<tr>
<td>CLINICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>PARAMETER</strong></td>
<td><strong>GRADE 1</strong></td>
<td><strong>GRADE 2</strong></td>
<td><strong>GRADE 3</strong></td>
<td><strong>GRADE 4</strong></td>
</tr>
<tr>
<td></td>
<td><strong>MILD</strong></td>
<td><strong>MODERATE</strong></td>
<td><strong>SEVERE</strong></td>
<td><strong>POTENTIALLY</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>LIFE-THREATENING</strong></td>
</tr>
<tr>
<td>Hypotension</td>
<td>NA</td>
<td>Symptomatic,</td>
<td>Symptomatic,</td>
<td>Shock requiring use of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>corrected with</td>
<td>IV fluids</td>
<td>vasopressors or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oral fluid</td>
<td>indicated</td>
<td>mechanical assistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>replacement</td>
<td></td>
<td>to maintain blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pressure</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Asymptomatic,</td>
<td>Asymptomatic,</td>
<td>Effusion with</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>small effusion</td>
<td>moderate or</td>
<td>non-life-</td>
<td>consequences (e.g.,</td>
</tr>
<tr>
<td></td>
<td>requiring no</td>
<td>larger effusion</td>
<td>threatening</td>
<td>tamponade) OR Urgent</td>
</tr>
<tr>
<td></td>
<td>intervention</td>
<td>requiring no</td>
<td>physiologic</td>
<td>intervention indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention</td>
<td>consequences OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effusion with</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>non-urgent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>intervention</td>
<td></td>
</tr>
<tr>
<td>Prolonged PR interval</td>
<td>PR interval</td>
<td>PR interval</td>
<td>Type II 2<strong>nd</strong></td>
<td>Complete AV block</td>
</tr>
<tr>
<td></td>
<td>0.21 – 0.25 sec</td>
<td>&gt; 0.25 sec</td>
<td>degree AV block</td>
<td></td>
</tr>
<tr>
<td>Prolonged QTC</td>
<td>Asymptomatic,</td>
<td>Asymptomatic,</td>
<td>Asymptomatic,</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>QTC interval</td>
<td>QTC interval</td>
<td>QTC interval</td>
<td>consequences, e.g.,</td>
</tr>
<tr>
<td></td>
<td>0.45 – 0.47 sec</td>
<td>OR increase</td>
<td>0.48 – 0.49 sec</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR increase</td>
<td>sec OR increase</td>
<td>or other associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sec OR increase</td>
<td>in interval &gt; 0.03 sec</td>
<td>serious ventricular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sec OR increase</td>
<td>in interval &gt; 0.05 sec</td>
<td>dysrhythmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sec above</td>
<td>≥ 0.06 sec above</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>baseline</td>
<td>baseline</td>
<td></td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>NA</td>
<td>Deep vein</td>
<td>Deep vein</td>
<td>Embolic event (e.g.,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thrombosis AND</td>
<td>thrombosis AND</td>
<td>pulmonary embolism,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No intervention</td>
<td>Intervention</td>
<td>life-threatening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>indicated (e.g.,</td>
<td>indicated (e.g.,</td>
<td>thrombus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anticoagulation,</td>
<td>anticoagulation,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>lysis filter,</td>
<td>lysis filter,</td>
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<tr>
<td></td>
<td></td>
<td>invasive</td>
<td>invasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>procedure)</td>
<td>procedure)</td>
<td></td>
</tr>
<tr>
<td>Vasovagal episode</td>
<td>Present without</td>
<td>Present with</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>loss of</td>
<td>transient loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>consciousness</td>
<td>of consciousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td>NA</td>
<td>Asymptomatic</td>
<td>New onset with</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>(congestive heart failure)</td>
<td>diagnostic finding AND</td>
<td>symptoms OR</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention</td>
<td>Worsening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>indicated</td>
<td>symptomatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>congestive heart failure</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
</tr>
</tbody>
</table>
## CLINICAL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Asymptomatic</td>
<td>Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)</td>
<td>Symptomatic despite intervention</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>NA</td>
<td>Symptomatic AND Medical intervention indicated</td>
<td>Radiologic, endoscopic, or operative intervention indicated</td>
<td>Life-threatening consequences (e.g., sepsis or perforation)</td>
</tr>
<tr>
<td>Constipation</td>
<td>NA</td>
<td>Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas</td>
<td>Obstruction with manual evacuation indicated</td>
<td>Life-threatening consequences (e.g., obstruction)</td>
</tr>
</tbody>
</table>

### Diarrhea

**Adult and Paediatric ≥ 1 year**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period</td>
<td>Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period</td>
<td>Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated</td>
<td>Life-threatening consequences (e.g., hypotensive shock)</td>
<td></td>
</tr>
</tbody>
</table>

**Dysphagia-Odynophagia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic but able to eat usual diet</td>
<td>Symptoms causing altered dietary intake without medical intervention indicated</td>
<td>Symptoms causing severely altered dietary intake with medical intervention indicated</td>
<td>Life-threatening reduction in oral intake</td>
<td></td>
</tr>
</tbody>
</table>

**Mucositis/stomatitis (clinical exam)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema of the mucosa</td>
<td>Patchy pseudomembranes or ulcerations</td>
<td>Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma</td>
<td>Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)</td>
<td></td>
</tr>
</tbody>
</table>

**Nausea**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent nausea resulting in decreased oral intake for 24 – 48 hours</td>
<td>Persistent nausea resulting in minimal oral intake for ≥ 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)</td>
<td>Life-threatening consequences (e.g., hypotensive shock)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pancreatitis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic AND Hospitalization not indicated (other than emergency room visit)</td>
<td>Symptomatic AND Hospitalization indicated (other than emergency room visit)</td>
<td>Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Proctitis (functional-symptomatic)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Potentially Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal discomfort AND No intervention indicated</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities OR Medical intervention indicated</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities OR Operative intervention indicated</td>
<td>Life-threatening consequences (e.g., perforation)</td>
<td></td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
</tr>
<tr>
<td>-----------------------------------</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>Transient or intermittent vomiting with no or minimal interference with oral intake</td>
<td>Frequent episodes of vomiting with no or mild dehydration</td>
<td>Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)</td>
<td>Life-threatening consequences (e.g., hypotensive shock)</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)</td>
<td>Alteration causing no or minimal interference with usual social &amp; functional activities</td>
<td>Alteration causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Alteration causing inability to perform usual social &amp; functional activities</td>
<td>Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Altered Mental Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)</td>
<td>Changes causing no or minimal interference with usual social &amp; functional activities</td>
<td>Mild lethargy or somnolence causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social &amp; functional activities</td>
<td>Delirium OR obtundation, OR coma</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptomatic ataxia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptomatic ataxia causing inability to perform usual social &amp; functional activities</td>
<td>Disabling ataxia causing inability to perform basic self-care functions</td>
<td></td>
</tr>
<tr>
<td>Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)</td>
<td>Disability causing no or minimal interference with usual social &amp; functional activities OR Specialized resources not indicated</td>
<td>Disability causing greater than minimal interference with usual social &amp; functional activities OR Specialized resources on part-time basis indicated</td>
<td>Disability causing inability to perform usual social &amp; functional activities OR Specialized resources on a full-time basis indicated</td>
<td>Disability causing inability to perform basic self-care functions OR Institutionalization indicated</td>
</tr>
<tr>
<td>CNS ischemia (acute)</td>
<td>NA</td>
<td>NA</td>
<td>Transient ischemic attack</td>
<td>Cerebral vascular accident (CVA, stroke) with neurological deficit</td>
</tr>
<tr>
<td>Developmental delay – Paediatric ≤ 16 years</td>
<td>Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
<td>Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
<td>Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
<td>Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Headache</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function</td>
</tr>
<tr>
<td>Insomnia</td>
<td>NA</td>
<td>Difficulty sleeping causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Difficulty sleeping causing inability to perform usual social &amp; functional activities</td>
<td>Disabling insomnia causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Neuromuscular weakness (including myopathy &amp; neuropathy)</td>
<td>Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing inability to perform usual social &amp; functional activities</td>
<td>Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation</td>
</tr>
<tr>
<td>Neurosensory alteration (including paresthesia and painful neuropathy)</td>
<td>Asymptomatic with sensory alteration or paresthesia causing no or minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing inability to perform usual social &amp; functional activities</td>
<td>Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Seizure: (new onset)</td>
<td>NA</td>
<td>1 seizure</td>
<td>2-4 seizures</td>
<td>Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)</td>
</tr>
<tr>
<td>- Adult ≥18 years</td>
<td>See also Seizure: (known pre-existing seizure disorder)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure: (known pre-existing seizure disorder)</td>
<td>NA</td>
<td>Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder</td>
<td>Change in seizure character from baseline either in duration or quality (e.g., severity or focality)</td>
<td>Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)</td>
</tr>
<tr>
<td>Seizure – Paediatric &lt; 18 years</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting &lt; 5 minutes with &lt; 24 hours post ictal state</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with &lt; 24 hours post ictal state</td>
<td>Seizure, generalized onset with or without secondary generalization, lasting &gt; 20 minutes</td>
<td>Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
</tr>
<tr>
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</tr>
<tr>
<td>Syncope (not associated with a procedure)</td>
<td>NA</td>
<td>Present</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Vertigo causing no or minimal interference with usual social &amp; functional activities</td>
<td>Vertigo causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Vertigo causing inability to perform usual social &amp; functional activities</td>
<td>Disabling vertigo causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchospasm (acute)</td>
<td>FEV1 or peak flow reduced to 70 – 80%</td>
<td>FEV1 or peak flow 50 – 69%</td>
<td>FEV1 or peak flow 25 – 49%</td>
<td>Cyanosis OR FEV1 or peak flow &lt; 25% OR Intubation</td>
</tr>
<tr>
<td>Dyspnea or respiratory distress</td>
<td>Dyspnea on exertion causing no or minimal interference with usual social &amp; functional activities</td>
<td>Dyspnea on exertion causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Dyspnea at rest causing inability to perform usual social &amp; functional activities</td>
<td>Respiratory failure with ventilatory support indicated</td>
</tr>
<tr>
<td>Adult ≥ 14 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric &lt; 14 years</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Joint pain causing no or minimal interference with usual social &amp; functional activities</td>
<td>Joint pain causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Joint pain causing inability to perform usual social &amp; functional activities</td>
<td>Disabling joint pain causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Stiffness or joint swelling causing no or minimal interference with usual social &amp; functional activities</td>
<td>Stiffness or joint swelling causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Stiffness or joint swelling causing inability to perform usual social &amp; functional activities</td>
<td>Disabling joint stiffness or swelling causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Bone Mineral Loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric &lt; 21 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia (non-injection site)</td>
<td>Muscle pain causing no or minimal interference with usual social &amp; functional activities</td>
<td>Muscle pain causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Muscle pain causing inability to perform usual social &amp; functional activities</td>
<td>Disabling muscle pain causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>NA</td>
<td></td>
<td>Asymptomatic with radiographic findings AND No operative intervention indicated</td>
<td>Symptomatic bone pain with radiographic findings OR Operative intervention indicated</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td><strong>GENITOURINARY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervicitis (symptoms)</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>For other cervicitis see Infection: Infection (any other than HIV infection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervicitis (clinical exam)</td>
<td>Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption &lt; 25% of total surface</td>
<td>Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface</td>
<td>Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 50 – 75% total surface</td>
<td>Epithelial disruption &gt; 75% total surface</td>
</tr>
<tr>
<td>For other cervicitis see Infection: Infection (any other than HIV infection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-menstrual bleeding (IMB)</td>
<td>Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination</td>
<td>Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle</td>
<td>Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle</td>
<td>Hemothage with life-threatening hypotension OR Operative intervention indicated</td>
</tr>
<tr>
<td>Urinary tract obstruction (e.g., stone)</td>
<td>NA</td>
<td>Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction</td>
<td>Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction</td>
<td>Obstruction causing life-threatening consequences</td>
</tr>
<tr>
<td>Vulvovaginitis (symptoms)</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
<td>Symptoms causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>For other vulvovaginitis see Infection: Infection (any other than HIV infection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginitis (clinical exam)</td>
<td>Minimal vaginal abnormalities on examination OR Epithelial disruption &lt; 25% of total surface</td>
<td>Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface</td>
<td>Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface</td>
<td>Vaginal perforation OR Epithelial disruption &gt; 75% total surface</td>
</tr>
</tbody>
</table>
## CLINICAL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCULAR/VISUAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>Asymptomatic but detectable on exam</td>
<td>Symptomatic anterior uveitis OR Medical intervention indicated</td>
<td>Posterior or pan-uveitis OR Operative intervention indicated</td>
<td>Disabling visual loss in affected eye(s)</td>
</tr>
<tr>
<td>Visual changes (from baseline)</td>
<td>Visual changes causing no or minimal interference with usual social &amp; functional activities</td>
<td>Visual changes causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Visual changes causing inability to perform usual social &amp; functional activities</td>
<td>Disabling visual loss in affected eye(s)</td>
</tr>
<tr>
<td><strong>ENDOCRINE/METABOLIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal fat accumulation</td>
<td>Detectable by study participant (or by caregiver for young children and disabled adults)</td>
<td>Detectable on physical exam by health care provider</td>
<td>Disfiguring OR Obvious changes on casual visual inspection</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>NA</td>
<td>New onset without need to initiate medication OR Modification of current medications to regain glucose control</td>
<td>New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification</td>
<td>Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Detectable by study participant or caregiver (for young children and disabled adults)</td>
<td>Detectable on physical exam by health care provider</td>
<td>Disfiguring OR Obvious on casual visual inspection</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Asymptomatic</td>
<td>Symptomatic causing greater than minimal interference with usual social &amp; functional activities OR Thyroid suppression therapy indicated</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities OR Uncontrolled despite treatment modification</td>
<td>Life-threatening consequences (e.g., thyroid storm)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Asymptomatic</td>
<td>Symptomatic causing greater than minimal interference with usual social &amp; functional activities OR Thyroid replacement therapy indicated</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities OR Uncontrolled despite treatment modification</td>
<td>Life-threatening consequences (e.g., myxedema coma)</td>
</tr>
<tr>
<td>Lipoatrophy (e.g., fat loss from the face, extremities, buttock)</td>
<td>Detectable by study participant (or by caregiver for young children and disabled adults)</td>
<td>Detectable on physical exam by health care provider</td>
<td>Disfiguring OR Obvious on casual visual inspection</td>
<td>NA</td>
</tr>
</tbody>
</table>

## LABORATORY

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
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<tbody>
<tr>
<td><strong>ENDOCRINE/METABOLIC</strong></td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
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<tr>
<td>Lipoatrophy (e.g., fat loss from the face, extremities, buttock)</td>
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<tr>
<td><strong>HAEMATOLOGY</strong></td>
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<tr>
<td>Standard International Units are listed in italics</td>
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</tr>
<tr>
<td>Absolute neutrophil count (ANC) [9, 44]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adult and Paediatric, &gt; 7 days</td>
<td>750 – 1,000/mm³</td>
<td>500 – 749/mm³</td>
<td>250 – 499/mm³</td>
<td>&lt; 250/mm³</td>
</tr>
<tr>
<td>OR</td>
<td>0.75 x 10⁹ – 1.0 x 10⁹/L</td>
<td>0.5 x 10⁹ – 0.749 x 10⁹/L</td>
<td>0.25 x 10⁹ – 0.499 x 10⁹/L</td>
<td>&lt; 0.250 x 10⁹/L</td>
</tr>
<tr>
<td>Fibrinogen, decreased</td>
<td>100 – 200 mg/dL</td>
<td>75 – 99 mg/dL</td>
<td>50 – 74 mg/dL</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>OR</td>
<td>1.00 – 2.00 g/L</td>
<td>0.75 – 0.99 g/L</td>
<td>OR</td>
<td>0.50 – 0.74 g/L</td>
</tr>
<tr>
<td>OR</td>
<td>0.75 – 0.99 x LLN</td>
<td>OR</td>
<td>0.25 – 0.49 x LLN</td>
<td>OR</td>
</tr>
<tr>
<td>Haemoglobin (Hgb)</td>
<td></td>
<td></td>
<td></td>
<td>Associated with gross bleeding</td>
</tr>
<tr>
<td>Adult and Paediatric ≥ 57 days (HIV POSITIVE ONLY)</td>
<td>8.5 – 10.0 g/dL</td>
<td>7.5 – 8.4 g/dL</td>
<td>6.50 – 7.4 g/dL</td>
<td>&lt; 6.5 g/dL</td>
</tr>
<tr>
<td>OR</td>
<td>5.24-6.23 mmol/L</td>
<td>4.62-5.23 mmol/L</td>
<td>4.03-4.61 mmol/L</td>
<td>&lt; 4.03 mmol/L</td>
</tr>
<tr>
<td>International Normalized Ratio of prothrombin time (INR)</td>
<td>1.1 – 1.5 x ULN</td>
<td>1.6 – 2.0 x ULN</td>
<td>2.1 – 3.0 x ULN</td>
<td>&gt; 3.0 x ULN</td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>5.0 – 10.0%</td>
<td>10.1 – 15.0%</td>
<td>15.1 – 20.0%</td>
<td>&gt; 20.0%</td>
</tr>
<tr>
<td>Prothrombin Time (PT)</td>
<td>1.1 – 1.25 x ULN</td>
<td>1.26 – 1.50 x ULN</td>
<td>1.51 – 3.00 x ULN</td>
<td>&gt; 3.00 x ULN</td>
</tr>
<tr>
<td>Partial Thromboplastin Time (PTT)</td>
<td>1.1 – 1.66 x ULN</td>
<td>1.67 – 2.33 x ULN</td>
<td>2.34 – 3.00 x ULN</td>
<td>&gt; 3.00 x ULN</td>
</tr>
<tr>
<td>Platelets, decreased</td>
<td>100,000 – 124,999/mm³</td>
<td>50,000 – 99,999/mm³</td>
<td>25,000 – 49,999/mm³</td>
<td>&lt; 25,000/mm³</td>
</tr>
<tr>
<td>OR</td>
<td>100,000 x 10⁹ – 124,999 x 10⁹/L</td>
<td>50,000 x 10⁹ – 99,999 x 10⁹/L</td>
<td>25,000 x 10⁹ – 49,999 x 10⁹/L</td>
<td>&lt; 25,000 x 10⁹/L</td>
</tr>
<tr>
<td>WBC, decreased</td>
<td>2,000 – 2,500/mm³</td>
<td>1,500 – 1,999/mm³</td>
<td>1,000 – 1,499/mm³</td>
<td>&lt; 1,000/mm³</td>
</tr>
<tr>
<td>OR</td>
<td>2,000 x 10⁹ – 2,500 x 10⁹/L</td>
<td>1,500 x 10⁹ – 1,999 x 10⁹/L</td>
<td>1,000 x 10⁹ – 1,499 x 10⁹/L</td>
<td>&lt; 1,000 x 10⁹/L</td>
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</table>

<table>
<thead>
<tr>
<th>CHEMISTRIES</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Standard International Units are listed in italics</td>
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</tr>
<tr>
<td>Acidosis</td>
<td>NA</td>
<td>pH &lt; normal, but ≥ 7.3</td>
<td>pH &lt; 7.3 without life-threatening consequences</td>
<td>pH &lt; 7.3 with life-threatening consequences</td>
</tr>
<tr>
<td>Albumin, serum, low</td>
<td>3.0 g/dL – &lt; LLN</td>
<td>2.0 – 2.9 g/dL</td>
<td>&lt; 2.0 g/dL</td>
<td>NA</td>
</tr>
<tr>
<td>OR</td>
<td>30 g/L – &lt; LLN</td>
<td>20 – 29 g/L</td>
<td>&lt; 20 g/L</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>1.25 – 2.5 x ULN&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.6 – 5.0 x ULN&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5.1 – 10.0 x ULN&lt;sup&gt;†&lt;/sup&gt;</td>
<td>&gt; 10.0 x ULN&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>NA</td>
<td>pH &gt; normal, but ≤ 7.5</td>
<td>pH &gt; 7.5 without life-threatening consequences</td>
<td>pH &gt; 7.5 with life-threatening consequences</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.25 – 2.5 x ULN</td>
<td>2.6 – 5.0 x ULN</td>
<td>5.1 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>1.25 – 2.5 x ULN</td>
<td>2.6 – 5.0 x ULN</td>
<td>5.1 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
<td>GRADE 2 MODERATE</td>
<td>GRADE 3 SEVERE</td>
<td>GRADE 4 POTENTIALLY LIFE-THREATENING</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td>Bicarbonate, serum, low</td>
<td>16.0 mEq/L – &lt; LLN 16.0 mmol/L – &lt; LLN</td>
<td>11.0 – 15.9 mEq/L 11.0 – 15.9 mmol/L</td>
<td>8.0 – 10.9 mEq/L 8.0 – 10.9 mmol/L</td>
<td>&lt; 8.0 mEq/L &lt; 8.0 mmol/L</td>
</tr>
<tr>
<td>Bilirubin (Total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult and Paediatric &gt; 14 days</td>
<td>1.1 – 1.5 x ULN</td>
<td>1.6 – 2.5 x ULN</td>
<td>2.6 – 5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
<tr>
<td>Calcium, serum, high (corrected for albumin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult and Paediatric ≥ 7 days</td>
<td>10.6 – 11.5 mg/dL 2.65 – 2.88 mmol/L</td>
<td>11.6 – 12.5 mg/dL 2.89 – 3.13 mmol/L</td>
<td>12.6 – 13.5 mg/dL 3.14 – 3.38 mmol/L</td>
<td>&gt; 13.5 mg/dL &gt; 3.38 mmol/L</td>
</tr>
<tr>
<td>Calcium, serum, low (corrected for albumin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult and Paediatric ≥ 7 days</td>
<td>7.8 – 8.4 mg/dL 1.95 – 2.10 mmol/L</td>
<td>7.0 – 7.7 mg/dL 1.75 – 1.94 mmol/L</td>
<td>6.1 – 6.9 mg/dL 1.53 – 1.74 mmol/L</td>
<td>&lt; 6.1 mg/dL 1.53 mmol/L</td>
</tr>
<tr>
<td>Cardiac troponin I (cTnI)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer</td>
</tr>
<tr>
<td>Cardiac troponin T (cTnT)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer</td>
</tr>
<tr>
<td>Cholesterol (fasting)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Paediatric &lt; 18 years</td>
<td>170 – 199 mg/dL 4.40 – 5.15 mmol/L</td>
<td>200 – 300 mg/dL 5.16 – 7.77 mmol/L</td>
<td>&gt; 300 mg/dL ≥ 7.77 mmol/L</td>
<td>NA</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>3.0 – 5.9 x ULN</td>
<td>6.0 – 9.9 x ULN</td>
<td>10.0 – 19.9 x ULN</td>
<td>≥ 20.0 x ULN</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1 – 1.3 x ULN</td>
<td>1.4 – 1.8 x ULN</td>
<td>1.9 – 3.4 x ULN</td>
<td>≥ 3.5 x ULN</td>
</tr>
<tr>
<td>Glucose, serum, high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfasting</td>
<td>116 – 160 mg/dL 6.44 – 8.88 mmol/L</td>
<td>161 – 250 mg/dL 8.89 – 13.88 mmol/L</td>
<td>251 – 500 mg/dL 13.89 – 27.75 mmol/L</td>
<td>&gt; 500 mg/dL &gt; 27.75 mmol/L</td>
</tr>
<tr>
<td>Fasting</td>
<td>110 – 125 mg/dL 6.11 – 6.94 mmol/L</td>
<td>126 – 250 mg/dL 6.95 – 13.88 mmol/L</td>
<td>251 – 500 mg/dL 13.89 – 27.75 mmol/L</td>
<td>&gt; 500 mg/dL &gt; 27.75 mmol/L</td>
</tr>
<tr>
<td>Glucose, serum, low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult and Paediatric ≥ 1 month</td>
<td>55 – 64 mg/dL 3.05 – 3.55 mmol/L</td>
<td>40 – 54 mg/dL 2.22 – 3.06 mmol/L</td>
<td>30 – 39 mg/dL 1.67 – 2.23 mmol/L</td>
<td>&lt; 30 mg/dL 1.67 mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>&lt; 2.0 x ULN without acidosis</td>
<td>≥ 2.0 x ULN without acidosis</td>
<td>Increased lactate with pH &lt; 7.3 without life-threatening consequences</td>
<td>Increased lactate with pH &lt; 7.3 with life-threatening consequences</td>
</tr>
<tr>
<td>LDL cholesterol (fasting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult ≥ 18 years</td>
<td>130 – 159 mg/dL 3.37 – 4.12 mmol/L</td>
<td>160 – 190 mg/dL 4.13 – 4.90 mmol/L</td>
<td>≥ 190 mg/dL 4.91 mmol/L</td>
<td>NA</td>
</tr>
<tr>
<td>PARAMETER</td>
<td>GRADE 1 MILD</td>
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<td>GRADE 3 SEVERE</td>
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</tr>
<tr>
<td>Paediatric &gt; 2 - &lt; 18 years</td>
<td>110 – 129 mg/dL 2.85 – 3.34 mmol/L</td>
<td>130 – 189 mg/dL 3.35 – 4.90 mmol/L</td>
<td>≥ 190 mg/dL ≥ 4.91 mmol/L</td>
<td>NA</td>
</tr>
<tr>
<td>Lipase</td>
<td>1.1 – 1.5 x ULN</td>
<td>1.6 – 3.0 x ULN</td>
<td>3.1 – 5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
<tr>
<td>Magnesium, serum, low</td>
<td>1.2 – 1.4 mEq/L 0.60 – 0.70 mmol/L</td>
<td>0.9 – 1.1 mEq/L 0.45 – 0.59 mmol/L</td>
<td>0.6 – 0.8 mEq/L 0.30 – 0.44 mmol/L</td>
<td>&lt; 0.60 mEq/L &lt; 0.30 mmol/L</td>
</tr>
<tr>
<td>Pancreatic amylase</td>
<td>1.1 – 1.5 x ULN</td>
<td>1.6 – 2.0 x ULN</td>
<td>2.1 – 5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
<tr>
<td>Phosphate, serum, low</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Adult and Paediatric &gt; 14 years</td>
<td>2.5 mg/dL – &lt; LLN 0.81 mmol/L – &lt; LLN</td>
<td>2.0 – 2.4 mg/dL 0.65 – 0.80 mmol/L</td>
<td>1.0 – 1.9 mg/dL 0.32 – 0.64 mmol/L</td>
<td>&lt; 1.00 mg/dL &lt; 0.32 mmol/L</td>
</tr>
<tr>
<td>Paediatric 1 year – 14 years</td>
<td>3.0 – 3.5 mg/dL 0.97 – 1.13 mmol/L</td>
<td>2.5 – 2.9 mg/dL 0.81 – 0.96 mmol/L</td>
<td>1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L</td>
<td>&lt; 1.50 mg/dL &lt; 0.48 mmol/L</td>
</tr>
<tr>
<td>Paediatric &lt; 1 year</td>
<td>3.5 – 4.5 mg/dL 1.13 – 1.45 mmol/L</td>
<td>2.5 – 3.4 mg/dL 0.81 – 1.12 mmol/L</td>
<td>1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L</td>
<td>&lt; 1.50 mg/dL &lt; 0.48 mmol/L</td>
</tr>
<tr>
<td>Potassium, serum, high</td>
<td>5.6 – 6.0 mEq/L 1.81 – 1.99 mmol/L</td>
<td>6.1 – 6.5 mEq/L 1.99 – 2.03 mmol/L</td>
<td>6.6 – 7.0 mEq/L 2.03 – 2.10 mmol/L</td>
<td>&gt; 7.0 mEq/L &gt; 2.10 mmol/L</td>
</tr>
<tr>
<td>Potassium, serum, low</td>
<td>3.0 – 3.4 mEq/L 0.97 – 1.13 mmol/L</td>
<td>2.5 – 2.9 mEq/L 0.81 – 0.96 mmol/L</td>
<td>2.0 – 2.4 mEq/L 0.65 – 0.80 mmol/L</td>
<td>&lt; 2.0 mEq/L &lt; 0.65 mmol/L</td>
</tr>
<tr>
<td>Sodium, serum, high</td>
<td>146 – 150 mg/dL 3.78 – 3.99 mmol/L</td>
<td>151 – 154 mg/dL 3.99 – 4.03 mmol/L</td>
<td>155 – 159 mg/dL 4.03 – 4.26 mmol/L</td>
<td>≥ 160 mg/dL ≥ 4.26 mmol/L</td>
</tr>
<tr>
<td>Sodium, serum, low</td>
<td>130 – 135 mg/dL 3.35 – 3.58 mmol/L</td>
<td>125 – 129 mg/dL 3.25 – 3.51 mmol/L</td>
<td>121 – 124 mg/dL 3.21 – 3.49 mmol/L</td>
<td>≤ 120 mg/dL ≥ 3.49 mmol/L</td>
</tr>
<tr>
<td>Triglycerides (fasting)</td>
<td>NA 0.50 – 0.59 mmol/L</td>
<td>500 – 750 mg/dL 5.65 – 8.48 mmol/L</td>
<td>751 – 1,200 mg/dL 8.49 – 13.56 mmol/L</td>
<td>&gt; 1,200 mg/dL &gt; 13.56 mmol/L</td>
</tr>
<tr>
<td>Uric acid</td>
<td>7.5 – 10.0 mg/dL 0.45 – 0.59 mmol/L</td>
<td>10.1 – 12.0 mg/dL 0.60 – 0.71 mmol/L</td>
<td>12.1 – 15.0 mg/dL 0.72 – 0.89 mmol/L</td>
<td>&gt; 15.0 mg/dL &gt; 0.89 mmol/L</td>
</tr>
</tbody>
</table>

**URINALYSIS**

*Standard International Units are listed in italics*

<table>
<thead>
<tr>
<th>Hematuria (microscopic)</th>
<th>6 – 10 RBC/HPF</th>
<th>&gt; 10 RBC/HPF</th>
<th>Gross, with or without clots OR with RBC casts</th>
<th>Transfusion indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria, random collection</td>
<td>1 +</td>
<td>2 – 3 +</td>
<td>4 +</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Proteinuria, 24 hour collection**

| Adult and Paediatric ≥ 10 years | 200 – 999 mg/24 h 0.200 – 0.999 g/d | 1,000 – 1,999 mg/24 h 1.000 – 1.999 g/d | 2,000 – 3,500 mg/24 h 2.000 – 3.500 g/d | > 3,500 mg/24 h > 3.500 g/d |
| Paediatric > 3 mo - < 10 years | 201 – 499 mg/m²/24 h 0.201 – 0.499 g/d | 500 – 799 mg/m²/24 h 0.500 – 0.799 g/d | 800 – 1,000 mg/m²/24 h 0.800 – 1.000 g/d | > 1,000 mg/m²/24 h > 1.000 g/d |

Comments: *Both amylase and lipase must be elevated to the same grade or higher (i.e. if total amylase is Grade 4, but lipase is only Grade 1, the Toxicity Grade is 1. In paediatric HIV patients, the most common source of serum amylase is the salivary glands. Salivary amylase elevations are generally not clinically significant. When amylase is released from damaged pancreatic cells, it can be a marker of pancreatitis. In most cases of clinical pancreatitis, lipase will also be elevated. However, lipase is also a non-specific marker. Combined elevation of amylase and lipase (each >5 x normal) often indicates pancreatic disease and requires evaluation. However, in the absence of pancreatic disease, drug can be resumed even at Grade 3 and 4 toxicity.*
If fasting values for C-peptide and serum insulin are above your centre’s normal ranges, please consult with an endocrinologist locally and report on the follow-up form.

**Basic Self-care functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence and feeding

**Basic Self-care functions – Young children:** Activities that are age and culturally appropriate (e.g. feeding self)

**Usual Social and Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social and Functional Activities – Young children:** Activities that are age and culturally appropriate (e.g. social interactions, play activities, learning tasks, etc).
APPENDIX 11: TANNER SCALES
The Five Stages of Female Breast and Pubic Hair Development
Breast and pubic hair development should be staged separately

<table>
<thead>
<tr>
<th>Stage</th>
<th>Female Breast</th>
<th>Pubic Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breasts during childhood. The breasts are flat and show no signs of development.</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Breast bud stage. Milk ducts and fat tissue forms a small mound.</td>
<td>Sparse, lightly pigmented, straight, medial border of labia.</td>
</tr>
<tr>
<td>3</td>
<td>Breasts continue to grow. Breasts become rounder and fuller.</td>
<td>Darker, beginning to curl, increased amount.</td>
</tr>
<tr>
<td>4</td>
<td>Nipple and areola form separate small mound. Not all girls go through this stage. Some skip stage 4 and go directly to stage 5.</td>
<td>Coarse, curly, abundant but amount less than in adult.</td>
</tr>
<tr>
<td>5</td>
<td>Breast growth enters final stage. Adult breast is full and round shaped.</td>
<td>Adult feminine triangle, spread to medial surface of thighs</td>
</tr>
</tbody>
</table>

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### The Five Stages of Male Genitalia and Pubic Hair Development

*Genitalia and Pubic hair should be staged separately*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Male Genitalia</th>
<th>Pubic Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Penis and testicles of a child. Testicles between 1 and 3 milliliters in volume.</td>
<td>No pubic hair.</td>
</tr>
<tr>
<td>2</td>
<td>First signs for penis and testicle growth; Testicles between 4 and 6 millilitres in volume.</td>
<td>Pubic hair beginning to grow; appears sparse and downy straight.</td>
</tr>
<tr>
<td>3</td>
<td>Penis continues to grow getting wider and longer. Testicles between 7 and 16 millilitres in volume.</td>
<td>Pubic hair appears curlier and coarser with increased pigmentation.</td>
</tr>
<tr>
<td>4</td>
<td>Penis continues to grow getting wider and longer. Testicles become larger. Penis gland or head is more developed. Testicles between 12 and 24 milliliters in volume.</td>
<td>Pubic hair becomes adult type, but less.</td>
</tr>
<tr>
<td>5</td>
<td>Penis growth enters final stage. Average erect penis length 6 1/4 inches. 90% are 5 - 7 inches. Glans penis or head is fully developed. Testicles 16 - 27 millilitres in volume. Testicles are about 1-3/4 inches.</td>
<td>Pubic hair is thick spreading to medial thighs.</td>
</tr>
</tbody>
</table>
APPENDIX 12: PENTA COMMITTEE STRUCTURE

PENTA Executive Committee

PENTA Steering Committee

Penta Project Management Team

Cohort Collaboration Executive Committees

Training Committee

Pharmacology Committee

Virology/Immunology Committee

Trials Centres:

- **MRC CTU** co-ordinates clinical sites in the UK, Ireland, Italy, Germany, Netherlands, Sweden, Brazil, Greece and Thailand (HIV-NAT)
- **INSERM** co-ordinates clinical sites in France, Belgium, Denmark, Spain, Switzerland, Portugal, Poland, Romania and Argentina
- **PHPT** co-ordinates PHPT clinical sites in Thailand

**Clinical site investigators**

Paediatric clinical centres participate in the PENTA network and enrol children in clinical trials