

PENTA 11 Trial Summary

1.1 Aim and Objectives

The overall aim of the PENTA 11 trial is to evaluate the role of planned treatment interruptions in the management of HIV infected children who have responded well to antiretroviral therapy.

The specific objectives are:

- To determine whether children with chronic HIV infection undergoing planned antiretroviral (ART) treatment interruptions are disadvantaged clinically, immunologically or virologically by periods of time off ART.
- To assess HIV-specific immune responses during and after interruptions of ART, compared with continuous ART, in an immunology/virology substudy (Appendix 10).

1.2 Design

An open, randomised, controlled phase II exploratory trial in HIV-1 infected children on antiretroviral therapy (ART) with HIV-1 RNA <50 copies/ml and

- in children aged 2-6 years: CD4 percent $\geq 30\%$
 - in children aged 7-15 years: CD4 percent $\geq 25\%$ and CD4 ≥ 500 cells/mm³
- to compare the effect of intermittent versus continuous antiretroviral therapy (ART) on disease progression, CD4 percent, HIV-1 RNA and toxicity in children in whom clinicians would consider interrupting treatment until
- in children aged 2-6 years: CD4 percent declines to below 20%
 - in children aged 7-15 years: CD4 percent declines to below 20% **or** CD4 declines to below 350 cells/mm³

Immunological and virological eligibility criteria must be met at the screening visit and at the prior visit between 1 and 4 months before; immunological re-start criteria should be confirmed on a second sample as soon as possible and **within 4 weeks**.

100 children will be randomised to continue on their current ART regimen or to a strategy of CD4-driven planned treatment interruption(s) (PTI) for 72 weeks. Children randomised to PTI will stop all ART, and will restart ART if the CD4 percent falls to <20% (age 2-6) or CD4 percent falls to <20%, or CD4 falls to < 350 cells/mm³ (age ≥ 7).

Children should spend no more than 48 weeks off therapy and should be restarted at their week 48 visit if they have not already reached the immunological restart threshold.

Once HIV-1 RNA is again suppressed <50 copies/ml and either CD4 percent has increased above $\geq 30\%$ (age 2-6) or CD4 percent $\geq 25\%$ and CD4 ≥ 500 cells/mm³ (age ≥ 7) ART should be interrupted again if these results are confirmed at 2 visits, 1- 3 months apart and the child has been back on therapy for at least 24 weeks.

Enrolment will take place over 24 months and follow-up will continue until the last randomised child has completed 72 weeks follow-up.

1.3 Population

100 HIV-1 infected children, aged 2 to 15 years old inclusive, on any ART regimen containing 3 or more drugs which they have taken for at least 24 weeks with confirmed (on 2 occasions at least one month apart) HIV-1 RNA <50 copies/ml and either CD4 percent $\geq 30\%$ (age 2-6 years) or CD4 percent $\geq 25\%$ and CD4 ≥ 500 cells/mm³ (age ≥ 7).

1.4 Primary Outcome

Any of

- CD4 percent <15% (age 2-6)
- CD4 percent <15% and CD4<200 cells/mm³ (age ≥7)
- new CDC stage C diagnosis
- death

1.5 Secondary Outcomes

- change in ART (defined as any change from the ART regimen at randomisation)
- acute retroviral syndrome (see section 9.7)
- ART-related grade 3 and 4 clinical and laboratory adverse events
- HIV-1 RNA ≥400 copies/ml at week 72 having received ART continuously for the preceding 12 weeks
- HIV-1 RNA ≥50 copies/ml at week 72 having received ART continuously for the preceding 12 weeks
- number of HIV mutations present at 72 weeks conferring resistance to drugs taken at entry or during the trial
- adherence to ART as assessed by caregiver completed questionnaire
- acceptability of the two strategies of ART administration to families as assessed by caregiver completed questionnaire

1.6 Follow-up

All children will be seen at weeks -2 and 0 (screening and trial entry/randomisation), 12, 24, 36, 48, 60 and 72. All children starting a PTI, and at least 20 children in the continuous therapy arm in the immunology/virology substudy, will also be seen at weeks 2, 4 and 8. CD4 and viral load measurements will be performed locally and plasma stored at each assessment.

Additional visits should be undertaken as clinically indicated (particularly in the PTI arm), and will be at the discretion of the clinician. Any child approaching a re-start threshold (i.e CD4% <22% or CD4 count <400 cells/mm³) should be seen every 4 weeks.

Children in the PTI group should remain off ART until they meet one of the following conditions:

- age 2-6 years: CD4% <20% (confirmed on a separate sample)
- age ≥7 years: CD4% <20% or absolute CD4 <350 cells/mm³ (confirmed on a separate sample)
- new or recurrent CDC stage C or severe stage B event
- the child has spent 48 weeks on the current PTI.

Any child who reaches a primary endpoint should restart immediately without a confirmatory test and should not undergo a further PTI:

- CD4% <15% (age 2-6)
- CD4% <15% and CD4 < 200 cells/mm³ (age ≥7),
- new CDC Stage C diagnosis

In addition children whose CD4 drops rapidly reaching re-start criteria within 10 weeks of stopping should NOT undergo further PTIs.

Children can undergo a further PTI, if, after at least 24 weeks back on therapy:

- age 2-6 years: the CD4 percent increases to ≥30% and HIV RNA is <50 c/ml (both at 2 visits, 3 months apart) or
- age ≥ 7 years: the CD4 percent increases to ≥25% and CD4≥500 cells/mm³ and HIV-1 RNA < 50 copies/ml (all at 2 visits, 3 months apart)

Children should be followed until the last randomised child has completed 72 weeks of follow-up. Children being followed after week 72 should be seen every 12 weeks if on the continuous arm and if randomised to PTI should continue to follow the PTI strategy and the appropriate follow-up schedule unless the clinician or the family have concerns which they should discuss with the Trials Centre.

1.7 Immunology/Virology Substudy

Children weighing over 10kg from specific clinical centres will also be enrolled into an immunology/virology substudy to assess the immune response to PTI compared with continuous therapy (at least 20 children from the continuous arm and as many as possible from the PTI arm). For children in these centres randomised to continuous therapy this will mean additional visits at 2, 4 and 8 weeks. Cell storage will be required at all time-points up to 24 weeks and then 6 monthly.

1.8 A Pharmacokinetic (PK)/ Virological Evaluation of stopping strategies within PTI in the context of resistance development

Children enrolled into the PTI arm who are taking “problematic” agents (NNRTI or 3TC, see glossary / section 4.3) will follow the guidelines set out in Appendix 11 to allow collection of information on PK and resistance following their stopping in the PENTA 11 trial. The number of children on those agents and randomised to a PTI is likely to be relatively small, making the option of a further randomisation inappropriate.