

10 March 2006

PENTA 11 Trial
Treatment Interruption in Children with Chronic HIV-Infection: The TICCH trial

Protocol Amendment 3 *generating*
Protocol Version 3.0

SUMMARY

This protocol amendment includes the following changes to the protocol.

- I. Increased safety measures:
 - Re-definition of criteria for restarting ART
 - Capping of time off ART
 - Minimum requirement for time back on ART before a further Planned Treatment Interruption (PTI)
 - Exclusion of children with rapid immunological decline from further PTI
 - Increased monitoring of children with:
 - CD4% < 22% or CD4 < 400
 - CD4% nadir before starting HAART ≤5%
 - previous AIDS diagnosis
- II. Removal of the cap on numbers of children in the immunology substudy in the PTI arm
- III. Exclusion of children positive for Hepatitis B surface antigen receiving either lamivudine or tenofovir.
- IV. PK substudy – updated information
- V. Extension of the recruitment period from 12 to 24 months
- VI. Acceptability questionnaire: modification of question and of timing of completion
- VII. Clarification of follow-up after week 72
- VIII. Minor updates

I. INCREASED SAFETY MEASURES

Rationale

Recent data from 2 large PTI trials in adults (SMART¹, TRIVICAN²) have shown that CD4-guided PTIs stopping ART with CD4 > 350 cells/mm³ and restarting when CD4 falls to < 250 cells/mm³ has a higher risk of disease progression or death (including myocardial infarction, stroke requiring surgery, severe renal or hepatic failure) in adults.

No data on PTIs is currently available in children, who will have to spend many more years on therapy, and whose immune reconstitution is different from adults.

Although the PENTA 11 treatment interruption strategy uses CD4 criteria for stopping and restarting of ART which are already higher than SMART or TRIVICAN, the protocol is being amended to reduce the risk of disease progression even further:

- *children should re-start ARTs following CD4% < 20% OR CD4 < 350 cells/mm³ (with confirmatory sample within 4 weeks)*

¹ El-Sadr W, Neaton J for the SMART Study Investigators: Episodic CD4-Guided Use of Antiretroviral Therapy is Inferior to Continuous Therapy: Results of the SMART Study. *13th Conference on Retroviruses and Opportunistic Infections Feb 5-8 2006, Denver, Abstract 106LB*

² Danel C, Moh R, Sorho S, Minga A, Anzian A, Ba-Gomis O, Gabillard D, Bissagnene E, Salamon R, Anglaret X, and ANRS 1269 Study Group: The CD4-guided Strategy Arm Stopped in a Randomized Structured Treatment Interruption (STI) Trial in West-African Adults: ANRS 1269 Trivacan Trial. *13th Conference on Retroviruses and Opportunistic Infections Feb 5-8 2006, Denver, Abstract 105LB*

- children should spend no more than 48 weeks off ART and at least 24 weeks back on ART before an subsequent PTI
- children on a PTI with CD4% <22% or CD4 <400 cells/mm³ should be monitored every 4 weeks
- children whose CD4 drops rapidly after the first PTI and who restart within 10 weeks of stopping ART should not re-interrupt.
- children who enter the trial with CD4% nadir before HAART ≤5% or with a previous AIDS diagnosis must be seen at weeks 2, 4, 8 and 12 when starting a PTI (a visit at week 18 should also be strongly considered

These changes affect the following sections of the protocol:

1.2	Design
1.6	Follow-up
1.9, 1.10, 1.11	Flowsheets
2.2	Intermittent therapy in adults
2.3, 2.4, 2.5	<i>(renumbered to 2.4, 2.5, 2.6)</i>
4.2	Schematic diagram
4.3	Trial interventions
5.1	Inclusion criteria
5.5	Screening procedure
6.2	The PTI group
6.2.1	Restarting ART for falling CD4% or CD4 in the PTI group
6.2.3, 6.2.5	<i>(renumbered to 6.2.4, 6.2.6)</i>
6.2.4	Follow-up after re-starting ART in the PTI group <i>(and renumbered to 6.2.5)</i>
7.1	Schedule for follow-up
Appendix 2	Information sheets

The following should also be added:

2.3 Further preliminary data from adult studies

Five large (270-5500 patients) randomised controlled trials assessing a variety of different interruption strategies presented data at the Conference on Retroviruses and Opportunistic Infections in February 2006 with varying results. Two of the five trials (SMART [49] (n=5500) and TRIVACAN [50] (n=325, in Cote D'Ivoire)), both assessing CD4-guided treatment interruptions stopping ART with CD4 >350 cells/mm³ and restarting when CD4 falls to <250 cells/mm³, were both stopped early by their DSMB for inferiority based on differences in the relative risk of clinical events between randomised arms. Although higher in the interruption arms, the absolute risk of AIDS/death was low – in SMART 1.5 per 100 person years at risk in the continuous therapy arm versus 3.7 in the intermittent therapy arm. Of note, unexpectedly the risk of myocardial infarction/stroke requiring surgery/severe renal or hepatic failure was also larger in the interruption arm in SMART than in the continuous therapy arm (68 events in PTI arm; 46 events in continuous arm; RR 1.5).

A third trial (STACCATO (n=430) [51]), which also had a CD4-guided interruption strategy, used a different CD4 threshold for restarting ART (<350 cells/mm³). No AIDS events occurred in this trial in either arm, and the STACCATO investigators concluded the interruption strategy was equivalent to continuous therapy.

The final two trials (ISS-PART (n=270) and WINDOW (n=400) [52, 53]) considered repeated fixed treatment interruptions (of 2-3 months) – both fixed interruption strategies were concluded as safe by their investigators.

References added to Section 17 References

*The following should be added at the end of **section 2.6 Rationale:***

CD4-guided treatment interruption stopping ART with CD4 > 350 cells/mm³ and restarting when CD4 falls to < 250 cells/mm³ has a higher risk of disease progression/death and myocardial infarction/stroke requiring surgery/severe renal or hepatic failure in adults, at least over 1-2 years. However, the likely duration of treatment and immune reconstitution are very different in children compared to adults.

Unstructured treatment interruptions are common in both adults and children; however, interruptions are even more pertinent for children than adults because

- the vast majority of HIV positive children are infected vertically: generally they start ART early in life (under 5 years of age) and will probably need to be treated for many more years than those infected as adults.
- this is more difficult to sustain and may put them at higher risk of long-term toxicity later in life, as they are treated with anti-HIV drugs as they grow. In addition, prolonged ART in childhood is resulting in many children having high levels of resistance by the time they reach adolescence. Because ART is often started early in children, it is possible that some children did not even need to have started ART – children who are well may not adhere very well and quickly develop resistance.
- children and adolescents have a much more active thymus than adults. Immune reconstitution has been demonstrated to occur predominantly with naive rather than memory T cells in children in contrast to adults where memory response predominates. Therefore there are a priori reasons to suspect that response to treatment interruptions may well differ as well – particularly with respect to immune activation and cytokine function – although any differences could be positive or negative

There are virtually no data even from observational studies on planned treatment interruptions in children. The treatment interruption strategy proposed in PENTA 11 is based on CD4 criteria for restart/stop of ART which are already higher than SMART so are likely to have lower risk. In addition, such a CD4-guided strategy can be modified to reduce risk of disease progression even further

- children with CD4 within 20% or 50 cells/mm³ of the restart threshold should be monitored more intensely, to ensure that CD4 do not fall much below the restart thresholds
- children should spend no more than 48 weeks off ART, and at least 24 weeks back on ART after interruption, to ensure that they have at least 33% exposure to beneficial effects of ART which are not mediated through CD4
- children whose CD4 drop rapidly after first interruption and restart within 10 weeks of stopping ART should not re-interrupt to avoid reoccurrence of such a drop.

The following section should be added:

6.2.3 Re-starting ART at 48 weeks in the PTI group

Children should not spend more than 48 weeks on a PTI. If a child is still on a PTI they should be restarted on ART at the week 48 visit.

*The following should be added at the end of **Appendix 1:***

Duration of interruption

Survival curves of the primary endpoint (AIDS/death) in the SMART trial [49] demonstrate that there was no difference in risk between the continuous and intermittent therapy arms up until at least 4 months after randomisation. Nevertheless, the events occurring after 4 months could still be related to interruptions of therapy (albeit shorter ones). There was no difference in relative risk overall in year one versus year two following randomisation.

However, the two trials of fixed length treatment interruptions (WINDOW [53] and PART[52], 2-3 months interruption) presented at CROI 2006 both showed no difference between continuous and intermittent therapy in the rate of clinical events. Further, the fixed interruption arm of the

TRIVACAN trial [50] was not stopped by their DSMB, and follow-up in this and the continuous therapy arm will continue to planned end of study.

Short (<4 month) interruptions would involve getting used to more frequent stop and restart of therapy which is likely to be more complicated for the families, mean more visits to clinic, increase the risk of development of resistance over repeated interruptions, and be less acceptable in children. However, in order to reduce the potential risk from an open-ended treatment interruption (the median duration off ART in SMART was around 20 months), a cap on the amount of time a child should spend off ART in any particular interruption in the PENTA 11 trial has been introduced. Any PTI should be limited to 48 weeks which is considered practical and acceptable to families and does not increase the potential risk of increased resistance with multiple stops and restarts of ART.

II IMMUNOLOGY SUBSTUDY

In order to maximise the information about immunological response to treatment interruptions in children, the immunology/virology substudy will recruit as many children as possible (weighing > 10kg) from centres able to measure RA/RO T cells who are randomised to PTI.

This affects the following sections of the protocol:

- 1.7 Immunology/virology substudy**
- 4.5 Immunology/virology substudy**

III CHILDREN WITH HEPATITIS B

Children positive for Hepatitis B surface antigen who are receiving either lamivudine or tenofovir are excluded from the protocol.

- 5.2 Exclusion criteria**

IV PHARMACOKINETIC SUBSTUDY

The PK/virology substudy has been updated following the ongoing analysis of data from children enrolled in this substudy.

- 1.9, 1.10, 1.11 Flowsheets**
- 4.3 Trial interventions**
- 6.2.5 Follow-up after re-starting ART in the PTI group**
- Appendix 11 A pharmacokinetic/ virological evaluation of stopping strategies within Planned Treatment Interruptions in the context of resistance development**

*The following should be added at the end of **Appendix 11**:*

Preliminary data (February 2006)

Preliminary data on 10 children (2 Caucasians, 3 Africans, 3 Asians and 2 mixed origin) stopping nevirapine with undetectable viral load showed that all 10 had plasma nevirapine levels <0.5 mg/l at day 7. However, at least two children had a detectable level according to the assay used (0.06, 0.064 mg/l) and as a variety of assays were used, it is possible that a few other children had very low nevirapine levels. These preliminary data suggest that adoption of staggered stop or replacement strategy for 7-14 days may be sufficient to avoid the development of resistance in suppressed children interrupting nevirapine.

Preliminary data on 7 children stopping efavirenz with undetectable viral load demonstrated that three had detectable levels at 14 days (0.14, 0.26, 0.29 mg/l): therefore current recommendations are that clinicians enrolling children stopping efavirenz into PENTA 11 should stagger stop or replace with a PI for at least 14 days.

All children interrupting NNRTIs should continue to be followed in this PK substudy.

V RECRUITMENT PERIOD

Due to the delay in rolling out the protocol to all interested countries and the temporary suspension of recruitment during January – March 2006 due to the review of data from adult studies and a review of PENTA 11 data by the DSMC, the recruitment period will be extended from 12 to 24 months.

- 1.2** **Design**
- 4.1** **Design of trial**

VI ACCEPTABILITY QUESTIONNAIRE

As all children will now be re-starting ARTs after a maximum of 48 weeks on a PTI it is considered more appropriate to ask carers, and young people, as appropriate, about the acceptability of a PTI strategy 2-4 weeks after resumption of therapy. Question 6 (carers) and question 5 (young people) have been modified.

- 1.9, 1.10, 1.11** **Flowsheets**
- 7.7** **Measures of acceptability of treatment strategy**
- Appendix 2** **Information sheets**
- Appendix 12** **Acceptability questionnaires**

VII FOLLOW-UP AFTER 72 WEEKS

Clarification is given: the randomised strategy should be followed until the last randomised child has completed 72 weeks' follow-up. Children 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.

- 1.6** **Follow-up**
- 4.2** **Schematic diagram**
- 6.2.5** **Follow-up after starting ART in the PTI group**

VIII MINOR UPDATES

- Contacts**
- 5.3** **Co-enrolment guidelines**
- 7.1** **Schedule for follow-up**
- Appendix 5** **Investigator's agreement to participate.**