Therapeutic Drug Monitoring in HIV-Infected Children Starting a New Anti-Retroviral Regime.

No registrations found.

Ethical review	Positive opinion
Status	Suspended
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20993

Source
NTR

Brief title
N/A

Sponsors and support

Primary sponsor: Paediatric European Network for Treatment of AIDS (PENTA)
Source(s) of monetary or material Support: Paediatric European Network for Treatment of AIDS (PENTA)

Additional funding provided by Glaxo Smith Kline

Intervention

Outcome measures

Primary outcome

The effect of the TDM strategies on the viral load in terms of change from baseline (start or switch of therapy) to 96 weeks.

Secondary outcome

1. The proportion of children who ever achieve plasma HIV-1 RNA <50 copies/ml, and who subsequently maintain plasma HIV-1 RNA <50 copies/ml to 96 weeks;

2. Toxicity and tolerability of HAART;

3. Adherence to HAART as assessed by caregiver completed questionnaire and CORALs;

4. Progression to new AIDS defining event or death;

5. Number of switches in antiretroviral therapy;

6. The development of new genotypic resistance mutations by 96 weeks;

7. Change in CD4 % and CD4 count from baseline to 96 weeks;

8. Number of children in target area for pharmacokinetic parameters after 12 weeks.

Study description

Background summary

Since the introduction of highly active antiretroviral therapy (HAART), the rate of progression to AIDS and HIV-1-related deaths has been substantially reduced among adults and children living in the Western world.

Two laboratory markers, plasma HIV-1 RNA levels and CD4+ T-cell counts, have become the basis for the prediction of clinical, virological and immunological responses in HIV-1 infected adults and children treated with HAART. However, only 50% of adults commencing HAART will achieve maximal viral suppression below the limit of 50 copies/ml, with even lower rates in antiretroviral therapy (ART) experienced patients who switch therapy.

Even in those responding to therapy, the risk of subsequent treatment failure is substantial. The relatively low rates of continued virological success can be attributed to two major sources: problems with adherence, and drug related factors including toxicity and pharmacokinetics.

These can both lead to inadequately sustained drug concentrations which in turn result in the appearance of HIV variants resistant to drugs in the long-term.

Assessments and procedures:

Follow-up will take place at weeks 4 and 12, then every 12 weeks. This schedule of assessments indicates the minimum for protocol completion and data recording.

However it is the investigator's responsibility to see children as frequently as necessary, particularly for the monitoring of adverse events.

Children in minimal or maximal TDM groups who require repeat PK after starting their new regimen will also have to attend clinic at week 8 for a dosage change. If the dose still requires alteration after the PK (pharmacokinetic curve) at week 12, this should be done 4 weeks later with a further PK 4 weeks after that. Children should be fasting at week 0, 48 and 96 in order to obtain fasting lipids, glucose, insulin and c-peptide values. Clinical examinationA clinical examination must be performed at screening, baseline and at all follow-up protocol visits.

At each visit the following should be recorded:

1. Body weight and height;

2. Tanner scales in children >9 years old;

3. Head circumference in children <2 years old;

4. Any adverse event ³ grade 2 since last protocol visit;

5. New HIV-related signs and symptoms since last protocol visit Antiretroviral therapyPrescriptions 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. Laboratory testsLaboratory tests for efficacy and safety monitoring will include:

1. Haematology:

Haemoglobin, MCV, platelets, white cell count, neutrophil and lymphocyte counts;

2. Biochemistry:

Creatinine, albumin, total bilirubin, ALT, AST, Alkaline Phosphatase, pancreatic amylase or total amylase + lipaseLipids/glucose (children should be fasting overnight)Triglycerides, total cholesterol, glucose, insulin, c-peptide, HDL and LDL cholesterol.

3. Lymphocyte subsets:

a. CD3 (absolute and percentage);

b. CD3+CD4 (absolute and percentage);

c. CD3+CD8 (absolute and percentage);

d. Total lymphocyte count (if measured by immunology laboratory);

4. Virology:

HIV-1 RNA (viral load). Resistance testingResistance testing should be performed on all pre-treated children, or children who have received prophylaxis to reduce mother to child transmission, at screening and on all children if therapy is to be switched any time during the trial.

Plasma for storage 4.0 ml of EDTA blood will be stored at baseline, weeks 48 and 96 for retrospective testing in a central laboratory of HIV-1 viral load, where necessary, viral resistance and other HIV or its treatment related tests as appropriate.

Therapeutic drug monitoring Children on the maximal TDM group will have 2.0ml taken at weeks 24, 72 and 96 and at week 12 unless the full PK curve has had to be repeated. 2.0 ml of heparinised blood per sample should be collected at weeks 4, 12, 24, 48, 72 and 96 for children on the minimal TDM group and at weeks 4, 12, 24, 48 and 96 for children on the no TDM group.

Samples will be analysed retrospectively for children in the no TDM group. Adherence support materialsAdherence questionnaires should be completed by carers, and children if appropriate, at baseline (if the child was pre-treated) and for all children at week 4, 12, 24, 48, 72, and 96.

The adherence materials will be evaluated by children, parents and HIV clinic staff at week 48 and 96.

Study objective

The effect of the TDM strategies on the viral load in terms of change from baseline (start or switch of therapy) to 96 weeks.

Study design

N/A

Intervention

Children randomised to group 1 will receive “maximal TDM”. A full pharmacokinetic curve will be generated at week 4 (and repeated at 48 weeks) involving observed dosing and a day admission with repeat pharmacokinetic sampling (5 samples over 8 hours (18 hours for once daily NNRTIs).

If the full curve shows that the observed dose was inadequate compared against population PK data, the dose will be revised by the PK investigator and the full curve will be repeated 8-weekly until the dose is correct. (It is estimated that 30% of children will require a repeat curve.) Subsequent follow-up TDM samples will be taken with routine blood in the clinic (after unobserved but reported intake at least 4 hours previously) and will be used to monitor adherence, assess the likelihood of drug interactions and to check for toxicity.
Children randomised to group 2 will receive “minimal TDM’. The week 4 single TDM sample will be taken at least 4 hours after reported but unobserved intake and will be used to check for adequate dosing against population PK data. The dose can be revised as advised by the PK investigator and the single TDM sample will be repeated 8-weekly until the dose is correct. Subsequent follow-up TDM samples will be taken with routine blood in the clinic (after unobserved but reported intake) and will be used to monitor adherence, assess the likelihood of drug interactions and control for toxicity, as for the maximal TDM group above.

Children randomised to group 3 will not receive any TDM results. All TDM samples will be analysed retrospectively at the end of the trial.

The week 4 single TDM sample will be taken at least 4 hours after reported but unobserved intake, to match samples taken from the “minimal” TDM group, and will be used to check for adequate dosing against population PK data at the end of the trial.

All subsequent scheduled TDM samples will be taken at least four hours after unobserved but reported intake with routine blood in the clinic. It is planned to recruit 166 children over 16 months.

All children will be followed until the last child enrolled has completed 96 weeks of follow-up. Caregivers will be asked to consent to regular clinic data being provided in annual long-term follow-up.

Contacts

Public
Reader in Epidemiology/Hon Consultant Paediatrician HIV Division MRC Clinical Trials Unit 222 Euston Road
Diana Gibb
222 Euston Road

London NW1 2 DA
United Kingdom
+44 (0)20 76704709
Scientific
Reader in Epidemiology/Hon Consultant Paediatrician HIV Division MRC Clinical Trials Unit 222 Euston Road
Diana Gibb

222 Euston Road

London NW1 2 DA
United Kingdom
+44 (0)20 76704709

Eligibility criteria

Inclusion criteria

1. Confirmed HIV-infected, i.e. positive plasma HIV-1 RNA or DNA test on two consecutive occasions (for children less than 18 months old), or positive HIV serology (for children aged 18 months and older) aged one month to 17 years inclusive;

2. Parents/guardians, and children where appropriate, are willing and able to give informed consent;

3. Plasma HIV-1 RNA viral load ³ 1000 copies/ml;

4. Pre-treated children, including children who have received antiretroviral therapy only as prophylaxis to reduce mother to child transmission, who are prepared to wait for the results of a resistance test before starting new therapy;

5. Starting antiretroviral therapy or switching to a new antiretroviral regimen considered likely to be highly active according to the results of a local resistance test, and containing either a PI or NNRTI or both; that is with:

a. Either 3 or more active drugs including a PI and/or NNRTI;

b. Or 2 active drugs: a boosted PI and an NNRTI.

Exclusion criteria

Grade 3 or 4 creatinine or liver function tests.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Recruitment

NL

Recruitment status:	Suspended
Start date (anticipated):	15-10-2004
Enrollment:	166
Type:	Anticipated

Ethics review

Positive opinion

Date:	09-09-2005
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL278

Register	ID
NTR-old	NTR316
Other	: N/A
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A