Dr Nick Paton
MRC Clinical Trials Unit, London

COMPETING INTEREST OF FINANCIAL VALUE £1,000:

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Nick Paton</td>
<td>No conflict of interest</td>
</tr>
</tbody>
</table>

Date: April 2012
Update on MRC adult HIV treatment trials

Nick Paton MD FRCP
MRC Clinical Trials Unit
BHIVA conference, April 2012

Summary

• MRC CTU strategy
• Current trials
• Future directions
MRC CTU trials - characteristics

• Large trials
  – Multi-centre
  – Often multinational
  – Require the expertise of an experienced coordinating centre
  – Occasionally smaller trials if likely to lead to definitive strategic trial

• Address important strategic questions applicable to large patient populations

• Designed to impact treatment guidelines

MRC CTU trials - characteristics

• “Take a long time” [..usually not short-term VL endpoints]

• Address scientific questions in sub-studies

• *Methodological innovation

• ** Relevance to global health [MRC strategy + funding opportunities]
Adult HIV treatment trials: 2010-15

- Optimising treatment in early chronic HIV disease
  - Early antiretroviral therapy
  - Immune based / anti-inflammatory therapy

- Optimising first-line therapy
  - Protease inhibitor monotherapy
  - Raltegravir-based dual therapy
  - Strategies to decrease early mortality in late presenters

- Optimising second-line therapy
  - Raltegravir-based dual therapy / PI monotherapy

- Trials in co-infections
  - Tuberculosis, Hepatitis B, Hepatitis C

1. Optimising treatment in early chronic disease
START rationale

The Broader Spectrum of HIV Disease
Ongoing Morbidity from HIV

CD4+ cells

Early Opportunistic Infections
Late Opportunistic Infections

Infection

Time in Years

START Design

HIV-infected participants with CD4+ cell counts > 500 cells/mm³

Early ART Group
Immediately initiate ART

Deferred ART Group
Defer ART until CD4+ <350 cells/mm³ or symptoms develop

Primary endpoint: AIDS + serious non-AIDS + death of any cause
<table>
<thead>
<tr>
<th></th>
<th>Goal</th>
<th>N</th>
<th>% of goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomics</td>
<td>As many as possible</td>
<td>1551</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>600</td>
<td>595</td>
<td>99</td>
</tr>
<tr>
<td>Inf. Consent.</td>
<td>2000</td>
<td>2034</td>
<td>102</td>
</tr>
<tr>
<td>Art. Elasticity</td>
<td>300</td>
<td>222</td>
<td>74</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1000</td>
<td>424</td>
<td>42</td>
</tr>
<tr>
<td>BMD</td>
<td>400</td>
<td>97</td>
<td>24</td>
</tr>
<tr>
<td>LFP</td>
<td>990</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

**HCQ-01 design**

Clinically stable; CD4 > 350

Randomise

- Hydroxychloroquine 2 x 200mg/day
- Placebo 2 x 200mg/day

Trial follow-up

Week 4, 12, 24, 36, 48

1st endpoint: CD8 activation (CD38+HLADR+)
2. Optimising first-line therapy

- PI monotherapy - PIVOT
- Raltegravir-based dual therapy – NEAT001
- Strategies to decrease early mortality in late presenters- REALITY
PIVOT design

Primary endpoint: Preservation of future drug options (i.e. no drug resistance)

On triple ART
VL < 50 for >6m
(n = 400)

Randomization 1:1

PI mono (n = 200)

PI mono (n = 200)

Triple therapy (n = 200)

Triple therapy

5y follow-up

*Patients return to triple therapy if VL >50 copies X 2 tests

Secondary endpoints

- Serious drug or disease-related complications
- Adverse events
- Viral load rebound
- CD4 count change
- Quality of life change
- Neurocognitive function change
- Health care costs
PIVOT

43 Participating Sites

Recruitment

Target and Actual Accrual and sites open for PIVOT

Recruitment Period

- Sites Open
- Actual Accrual
- Target Accrual (18m)
Follow-up

- Withdrawals: 4 (<1%)
- Visits not attended
  - 0: 86%
  - 1: 9%
  - 2: 3%
  - >=3: 2%
- DMC March 2012: no safety concerns
- Continue follow up to end 2013

NEAT 001 – Outline

ARV Naive HIV+ patients
ART indicated by national guidelines

RANDOMISATION
800 patients

- DRV/r + TDF/FTC
- DRV/r + Raltegravir

Follow-up until last patient reaches 96 weeks

PRIMARY ENDPOINT: Time to clinical or virological failure
NEAT

- 41 partner institutions
- 16 European Countries
- over 350 affiliated sites
- Funded by EU
- AIM= to strengthen European Clinical Research Capacity

Location of one or more NEAT partner institutions

REALITY

Reduction of EArly mortaLITY in HIV-infected adults and children starting antiretroviral therapy
Background

![Graph showing comparison of mortality in months after starting HAART in low-income and high-income settings.]

Figure 2: Comparison of mortality in the months after starting HAART in low-income and high-income settings

Interventions to reduce early mortality after starting HAART

- More potent ART
- Preventing early infections
  - Antibiotics
  - TB prophylaxis: INH
  - Antifungal prophylaxis
  - De-worming at starting ART
- Extra Nutrition

Lancet 2006; 367: 817-24
Study Design

- 2x2x2 open-label factorial design
- 1800 adults and children
- Kenya, Malawi, Uganda, Zimbabwe
- 48 weeks follow up
- Primary endpoint: mortality

HIV-infected adult, adolescent or child aged 5 years or older; Naïve to ART (apart from drugs for prevention of MTCT); CD4 T-cell count <100 cells/mm² on screening blood test

All patients enter the three randomisations A, B, C simultaneously

RANDOMISE (A)

Standard 2 NRTI+NNRTI plus integrase inhibitor for 12 weeks

Standard 2 NRTI+NNRTI

RANDOMISE (B)

Enhanced prophylaxis with cotrimoxazole, isoniazid, fluconazole plus 5 days azithromycin and single dose albendazole

Standard cotrimoxazole prophylaxis (all patients) plus isoniazid from 12 weeks (not Malawi as not in guidelines)

RANDOMISE (C)

12 weeks Ready-to-Use Supplementary Food (RUSF)*

Standard nutritional support*

* all patients meeting criteria for Ready to Use Therapeutic Food will receive this, regardless of randomisation
3. OPTIMISING SECOND-LINE THERAPY

ERNEST

Europe-Africa Research Network for Evaluation of Second-line Therapy

ERNEST Rationale

• In African rollout settings, failure on 2NRTI + NNRTI often a/w extensive resistance
• 2nd line SOC = PI/r + 2NRTI ….but contribution of 2NRTIs uncertain
• No evidence from RCTs for 2nd line
• AIM: to determine optimal 2nd line treatment in a setting relevant to the public health rollout-approach to HIV Rx
**EARNEST Trial design**

**1200 ELIGIBLE PATIENTS (failed 1st line NNRTI-based Rx)**

**RANDOMIZE**

- **bPI + 2 NRTI**
  (NRTIs according to local standard of care)

- **bPI + RAL**
  (12wk induction)

- **bPI**
  (Monotherapy)

**FOLLOW-UP FOR 144 WEEKS**

**Primary Outcome – Good HIV disease control – defined as:**
- No new WHO Stage 4 events by week 96 AND
- CD4 cell count > 250 cells/mm³ at wk 96 AND
- VL < 10,000 copies/ml OR
- VL >10,000 copies/ml with no PI resistance mutations (wk 96)

**EARNEST sites**
4. TRIALS IN CO-INFECTIONS

- Tuberculosis
  - Rifaquine
  - ReMoxTB
  - STREAM
- Hepatitis B
- Hepatitis C
8-21 years old, on 2NRTI+EFV first line regimen with VL<50 for 1 year or more (n = 160)

Continuous (n=80)

SCT
5 days on; 2 days off (n=80)

Endpoint: VL > 50 copies/ml at 48 weeks

e-mail PENTA@ctu.mrc.ac.uk or talk to STEVE WELCH

Summary of future directions

• For adult HIV treatment ……
  – Comprehensive portfolio of active studies
  – Few big strategic treatment questions left
  – Future funding mainly directed to global health
  – Focus will shift to co-infections and to resource-limited settings

• Prevention…….