United Kingdom
Community Advisory Board (UK CAB)
HIV treatment advocates network

CAB 28 - Meeting Report
30 January 2009

Contents:

Presentations are all available from the website for the January 2009 meeting
http://www.ukcab.net/jan09/index.html

Attendees:

Andrew Kpau	Leeds Skyline Service	Leeds
Akpane Catherine Essoh	AHPN	London
Anthony Tukai	Oxfordshire County Council	Oxford
Badru Male	CHAT	London
Bradley Smith	MESMAC	Yorkshire
Ben Cromaty	North Yorkshire AIDS Action	Yorkshire
Emma Hudson	Brunswick Centre	Halifax
Edwin Bernard	NAM	Brighton
Elijah Amooti	African Eye Trust	London
Jeff Ukiri	Black Health Agency	Manchester
Joram Barigye	THT Woking	Surrey
Kingsley Oturu	Inst for Int. Health & Dev	Edinburgh
Memory Sachikonye	UKCAB	London
Michael Marr	Waverley Care	Edinburgh
Nakamba Ng'ambi	Leeds Skyline Service	Leeds
Nyambe Mukelebai	Leeds Skyline Service	Leeds
Paul Clift	King's College Hospital	London
Richard Day	MESMAC	Yorkshire
Robert James	UKCAB	London
Samuel Serunjogi		London
Winnie Sseruma	HIV i-Base	London

Programme:

09.45-10.00	Coffee, registration and expenses
10.00-10.15	Welcome and announcements
	Updates: BHIVA Rep, SG membership
10.15-10.30	Brief look at use of the UKCAB membership forum
10.30-10.45	Feedback: "Late Presenters" - BMS/Gilead patient education programme
10.45-11.00	Refreshment break
11.00-11.15	Conference feedback from HIV9
11.15-12.00	Immunology - Dr Adrian Palfreeman, Consultant HIV Physician
12.00-12.30	HIV Trials Update - Nick Paton
12.30-14.00	Lunch
14.00-15.00	Tibotec - Etravirine, Darunavir and pipeline HIV plus HCV and TB
15.00-15.15	Refreshment break
15.15-15.45	Tibotec Q & A session
15.45-16.00	UK-CAB
	AOB
16.00	Close

UPDATES

- Roger Pebody is the new BHIVA Representative on the Audit Standards Committee and will be taking over from Gus Cairns when his term runs out. BHIVA is actively looking for a community rep on the Fundraising committee; any interested members should contact the BHIVA chair or the Secretariat.
- UKCAB is still looking for Steering Group members; the current Steering Group will consider applications from interested members.
- Robert James announced his resignation from the Steering Group due to work commitments, will continue to attend CAB meetings.
- A brief demonstration on the use of the forum was done by Michael and urged all members to post and contact Memory if they encounter any problems.
- Michael reported that he found the Young Children's presentations from last meeting very useful as it fits in with line of work, supporting young children

FEEDBACK

- Late presenters – BMS/Gilead patient education programme: Michael and Memory had attended a meeting during HIV9 conference in Glasgow. This is a programme designed to train treatment advocates to encourage people to test early and start treatment early. Different issues in Europe include – immigration, social, etc. The aim is to support people to have best treatment options. Question raised is: Does UKCAB want to be part of it, given experiences from some members who had been involved is similar programmes?

Discussion:

- Ben Cromaty reported that he went to a meeting on testing and was discouraged by the effort to do things on a Pan-European basis.
- Paul Clift noted that whoever joins the BMS/Gilead SG should be politically aware of such intentions. It could be valuable if the terms are agreed on.

Comment: Do we want someone to come and talk to UKCAB about late presentation? Would love to see some initiatives with GPs who do not see the obvious signs.

Comment: New HIV testing guidelines that highlight for picking up symptoms at a primary care level. Rural community is a different world to identify symptoms. What can UKCAB do to help in training GPs to identify symptoms?

Q: Is there any legislation in the pipeline for compulsory testing?
A: No.

Michael mentioned that it would be an opportunity for capacity building for members, need to find innovative ways of advocating the effectiveness of starting treatment early.

CAB members attending meetings and conferences urged to inform the forum so there is a comprehensive list of activities UKCAB is involved in.

Edwin Bernard had attended the launch of a new report by the Terrence Higgins Trust (THT) at the House of Commons that has revealed a systematic mishandling of complaints for alleged criminal HIV transmission in England & Wales. The report, *Policing Transmission* was welcomed by the Association of Chief Police Officers (ACPO), which acknowledged that "too many times we have got it wrong". Need to produce guidance for police on how to deal with this. Feedback any case studies to NAT.

Full article:

http://www.aidsmap.com/en/news/E812EE99-35E0-4323-9203-8781E4639135.asp?type=preview

PDF or the report:
http://www.tht.org.uk/informationresources/publications/policyreports/policingtransmission950.pdf

Comment: Christian Aid are doing research of criminalisation of HIV around the world, could be compared to what is happening in the UK.

NAT has archives of HIV criminalisation trials in England and Wales.

A webcast from one community session from HIV9 conference was shown and members encouraged to visit the HIV9 website in their own time. Gus' presentation at HIV9 will also be available on the UKCAB website shortly.

Immunology: A rough guide – Dr Adrian Palfreeman

There are two main types of T-cells. T-4 cells, also called CD4, are "helper" cells. They lead the attack against infections. T-8 cells (CD8) are "suppressor" cells that end the immune response. CD8 cells can also be "killer" cells that kill cancer cells and cells infected with a virus.

CD4 Lymphocytes (T helper cells):
- Coordinate much of the immune response to micro-organisms
- Help B-cells respond to foreign proteins
- Secrete substances that enable CD8 T-cells to proliferate
- Activate macrophages so that they can kill certain organisms, including some organisms associated HIV infection.

CD8 Lymphocytes (Cytotoxic T cells)
- Kill cells in the body identified as abnormal or foreign
- Tumour cells
- Tells that have been infected by viruses.

How does HIV reduce CD4 Cells?
- Increased turnover of cells in response to infection
- Trapping of HIV in lymph nodes
- Shortened survival of CD4 cells
- Reduced production of new cells
- Reduction of T cell progenitor production from bone marrow

Natural killer (NK) cells are critical components of immune system function. Research shows that low NK cell activity is present in nearly all illnesses. NK cells defend the body against attack by foreign invaders. NK cells are non-specific, meaning they attack any target including bacteria, tumor or virally infected cells. The NK's ability to randomly attack a wide range of foreign invaders is the basis of the name "natural killer" cell.

Q: Why does HIV attack CD4 cells?
A: It attacks most cells. CD4 cells have in increased turnover in response to infection and have a short life-span. They are the most in the body, mainly in the lymph nodes.

INTERLEUKIN-2 (IL-2) is a protein made by the body. T-helper cells, a kind of white blood cell, produce IL-2 when they are stimulated by an infection. IL-2 makes infection-fighting cells

multiply and mature. Patients who use IL-2 have large increases in their CD4 cell counts and given as an intravenous infusion and as twice-daily subcutaneous (below the skin) injections. IL-2 causes irritation where the injections are given and flu-like symptoms.

Q: Is anyone here on IL-2?
A: No.
Don't know if IL-2 will help patients whose CD4 is not rising.

Q: Why has there been a difficulty in coming with an HIV vaccine?
A: Efforts have not been successful, antibodies are not recognised by the immune system. Who do give the vaccine to - preventative or those infected? Hep B vaccine is effective but poorly delivered in the UK. No vaccine manufactured yet, drug do work however.

Stem cell research may answer a lot of the chronic diseases, but not sure how it will work in HIV.

Q: Will stem cell research be an alternative therapy such as lymphatic drainage?
A: May work, but may cause problems like septicemia.

New MRC HIV Clinical Trials Update – Nick Paton, MRC

ESPRIT and SILCAAT: Does IL-2 induced CD4 count increase give clinical benefit?

HCQ-01- can it decrease immune activation in HIV infection?
- 32 patients screened, 10 randomised, sites say it is difficult to identify pts as they do not attend clinic regular. May look for community involvement.

PIVOT – monotherapy to reduce long-term toxicity?
- To look at resistance and toxicity after 5 years. Sub-studies: CNS viral replication, genital secretion VL, body composition, immune activation. Trial will recruit 400 patients.

Q: Can doctors at clinics not taking part in the research still recruit patients?
A: Not all consultants are aware of research and some pts may not see the same consultant.

Comment: Some clinics have an email service and could offer trial opportunities to patients

Q: Could HCQ be used in people with low CD4 to combat IRIS?
A: Only alternative is to use ART, could get complicated with multi-drug interactions. New sites for clinical trials being set up, nothing in the north of England because they samples need to get to the lab in 4hrs, will be considered in future.

Q: Who is being targeted?
A: African communities have had experience in taking chloroquine, will also contact African Eye Trust.

PIVOT – monotherapy to reduce long-term toxicity.
- To look at resistance and toxicity after 5 years. Sub-studies: CNS viral replication, genital secretion VL, body composition, immune activation. Trial will recruit 400 patients.

Q: Does one need no pre-existing resistance to a PI?
A: You need to be on 1st line regiment that has not failed.

Comment: Thoughts on patient recruitment; they may need focus groups so they can understand what the trial is about. MRC can hold such workshops.

Tibotec - 4 presentations on: Updates on Darunavir, Etravirine, TMC278, TMC207, HCV pipeline

Update on Darunavir: Dr Perry Mohammed

- Once daily dosing for treatment currently licensed for treatment experienced patients. 200 patients in study on 800mg/day.
- ODIN study: 48 weeks treatment in 612 pre-treated patients on stable HAART whose viral load was greater than 1000 copies/ml and no resistance to Darunavir
- Monet study - European monotherapy is in 13 countries with 250 patients

Q: Any experience of danuravir on monotherapy?
A: Yes, most patients still have an undetectable viral load.

Q: Any study to do comparative study?
A: No

New Danuravir dosing formulations:

- For treatment-experienced patients: 100mg RTV capsule and 600mg DRV tablets (currently 2 x 300mg tablets)
- For treatment-naïve patients: 100mg RTV capsule and x400mg DRV.

There has been a request for smaller 75mg for patients who cannot swallow the big one, still working on that.

Q: Any solution formula for paeds?
A: This is in development.

Q: Is there also a formulation for young people who have adherence issues?
Comment: Maybe you should look into making flavoured solutions for paeds.

Q: Why are there no injectable formulations?
A: We tried. Tables are film coated and can be crushed or broken in half.

Q: What are the side effects?
A: Less diahorrea than kaletra although HDL cholesterol maybe slightly higher .

Q: Any different ideas on packaging? Would prefer blister packs for ease of carrying around.
A: No yet, all the medication is currently in bottles.

Etravirine (ETR) Update: Rekha Sinha, MD
Patients recruited from Thailand, Australia, Europe and the Americas. Phase III [see http://www.i-base.info/manual/en/8-4.html) trial.

- Safety and Tolerabilty: 61% of patients in the ETR group achieved a confirmed undetectable viral load compared with the 40% in the placebo group.
- Adverse events:
    - Rash – usually mild to moderate and infrequently led to permanent discontinuation.
    - Nervous system and psychiatric disorders – no increased risk on patients with a psychiatric history; abnormal/nightmare dreams similar in incidence to placebo;

no episodes of hallucination, suicidal ideation or manic symptoms. Side effects similar incidence to placebo, low severity, did not lead to discontinuation.
    - Hepatic and lab abnormalities – similar incidence to placebo, low severity, did not lead to discontinuation.

Conclusions: generally safe, no severe adverse events due to use of ETR.

Safety in Paediatric formulations: 40 treatment experienced children, stable on ARV and virologically suppressed. Common adverse events:

- Infections and infestations – rhinitis
- Nervous system disorders – headache
- Gastrointestinal disorders – diarrhoea, nausea
- Skin and subcutaneous disorders – rash, maculopapular rash

Conclusion: recommended dose per weight band for children and adolescents aged between 6 and 17 inclusive will be based on 5.2mg/kg.

Planned Trials with ETR:

- ETR, raltegravir plus ETC in HIV-infected early treatment-experienced patients. Objective: To assess the percentage of early treatment experienced HIV patients whose CD4 is less that 50 copies/ml at week 24
- **S**tudy of **E**favirenz **N**europsychiatric **S**ymptoms vs **E**TR (SENSE). Objectve: to compare neuropsychiatric adverse event profile of ETR vs EFV in combination with 2 N(t)RTIs at week 12
- ETR in a Nucleoside Sparing Regimen. Objective: Efficacy of ETR given in a PI containing N(t)RTI-sparing regimen in terms of the proportion of subjects achieving a plasma viral load of less than 50 copies/ml at week 24.

Q: What are your key sites for trials?
A: We are looking multi-centre trials.

ETR Resistance

- List of 44 NNRTI Resistance Associated Mutations (RAMs) was expanded to 57 by addition of all mutations at NNRTI resistance amino acid positions.
- Increasing ETR FC associated with a gradual loss in virological response

Q: Why can't you have film coating on ETR, it crumbles easily when once put in the mouth or handled with slightly moist hands?
A: It is challenging as coating increases its crystalisation, this is being looked into.

Q: Can the paeds formulation be dissolved in water?
A: Yes and has to be taken with meals.

Q: Does matter what kind of food?
A: No.

TMC278 Update: Peter Williams

- C204 study: See slides (http://www.ukcab.net/resources/presentations.html)
    - Ongoing (extended to 5 years), randomised, active-controlled, dose-ranging Phase IIb study in ARV-naïve patients
    - TMC278 blinded for all three groups until Week 96 versus open-label EFV

- Primary objective to evaluate the TMC278 efficacy (ITT-TLOVR) and safety dose-response relationship at Week 48

- TMC278 high and sustained virological response rate over 96 weeks
- A limited number of patients experienced virological failure and developed RAMs on TMC278-based therapy:
  - Very few patients experienced virological failure
  - The proportion of patients with treatment failure (viral load >1,000 copies/mL) developing treatment-emergent NNRTI RAMs was similar across groups
  - Eight different NNRTI RAMs in nine patients receiving TMC278
  - Two NNRTI RAMs in three patients receiving EFV
  - Resistance findings to be explored further in Phase III trials

Conclusions:

- All doses of once-daily oral TMC278 demonstrated a high and sustained virological response rate over 96 weeks
- TMC278 was generally safe and well tolerated
- Incidences of any grade 2–4 AE possibly related to treatment, rash, neurological- and psychiatric-related AEs and increases in lipids were lower with TMC278 than with EFV
- Efficacy and safety of TMC278 were well maintained between 48 and 96 weeks
- No definitive TMC278 resistance profile could be determined from the limited number of virological failures
- TMC278 is being further evaluated in Phase III trials at a dose of 25mg once-daily (qd)

Q: Have there been any incidents overdoes?
A: There was one incident and had no clinical threat.

Q: Is Kivexa good or bad, given the earlier reported heart problems?
A: No definite answers but would recommend starting on Truvada.

Q: Is there any significant difference between TMC278 and ETR?
A: Not recommended to give TMC278 in failed patients.

ECHO and THRIVE – phase III studies:

ECHO - ARV naïve patients:

- Randomized, double blind, double dummy
- Non-inferiority, primary efficacy endpoint % of subjects with viral load <50 HIV-1 RNA copies/mL (TLOVR),
- ARV-naïve subjects, primary NNRTI resistance excluded
- Backbone fixed to tenofovir + emtricitabine

THRIVE – ARV naïve patients

- Randomised, double blind, double dummy
- Non-inferiority, primary efficacy endpoint % of subjects with viral load <50 HIV-1 RNA copies/mL (TLOVR)
- ARV-naïve subjects, primary NNRTI resistance excluded
- Backbone WAS fixed to abacavir + lamivudine
- Positive test result for HLA-B*5701 excluded

TMC New Formulations

TMC278 for children
- Oral formulation to allow dosage adjustment by bodyweight in younger children
- Relative bioavailability study of 3 concept formulations ongoing

TMC278 LA
- Once-monthly injectable formulation
- Maintenance therapy with a companion injectable ARV
- Pre-exposure prophylaxis

Conclusions on TMC278 LA:
- Injectable LA formulations may provide a new paradigm in ARV use and may facilitate long-term compliance
- TMC278 LA is a promising depot formulation; the concept is viable
- Single 400mg and 600mg doses gave prolonged TMC278 plasma exposure of approximately 20ng/mL after 8 weeks
- PK exposures were comparable after IM and SC injections
- Favourable safety and tolerability: no serious AEs, grade 3 or 4 AEs or rash
- Injections were well tolerated, particularly when administered IMg; indurations were more frequent after SC than after IM injections
- Placebo injections were better tolerated than injections with TMC278 LA; 600mg IMg injections were better tolerated than 600mg SC and than 400mg IMd injections

Next steps: to perform a multiple-dose trial in HIV-negative healthy volunteers; continue with IM and SC (allowing self-administration) injections

Q: Any chance of getting TMC278 through IV?
A: No, it works better through intramuscular or subcutaneous injections.

Interim analysis of a double-blind, placebo-controlled study with TMC207 in patients with MDR TB: Karel de Beule

Trial design: Phase II, placebo-controlled, double-blind; patients with newly diagnosed smear positive MDR-TB. Stratified by trial site and degree of lung cavitation

2 stage trial design
- Stage 1 - Safety and dose determination
    - 8 weeks dosage TMC207/placebo and BR, then BR and 24 months follow-up
    - Dose regimen: 400 mg qd for 2 weeks followed by 200 mg three times weekly for 6 weeks
- Stage 2 - Recruiting - full 6 month dosage

Inclusion/Exclusion Criteria:
- Male and female 18-65 years
- Positive sputum smear $\geq$ 1+
- Confirmed resistance to H and R
- HIV negative or HIV+ with CD4+ > 300 and no ART
- No previous 2nd line anti-tuberculosis agents
- No significant extrapulmonary TB or concomitant illness

Conclusions:
- TMC207 was safe and well-tolerated over 8 weeks
- Dosing regimen validated for Stage 2
- 400 mg qd for 2 weeks followed by 200 mg tiw
- Addition of TMC207 to a 5-drug MDR-TB regimen resulted
- In faster culture conversion within 8 weeks
- In a higher conversion rate at week 8 - 47.5% TMC207 vs 8.7% placebo

Pipeline and HCV

TMC435 Hepatitis C
- Phase II-a, small cohorts, cohort 5. News @ EASL
- Phase II-b later in 2009

RSV353 (Respiratory Syncitial Virus)
- Phase I

Hepatitis C: Telaprevir
- Co-development with VERTEX.

ADVANCE study
- Sponsored and managed by ***Vertex***
- 1050 Treatment-naïve patients.

REALIZE study
- Sponsored and managed by TIBOTEC
- 650 Treatment-failure patients

Studies for HIV/HCV co-infected patients:
- DDI studies ongoing. Tenofovir: no significant interaction
- Co-infection study: pilot study will start this year
    - Synopsis of protocol has been sent to ECAB for review
    - US Community has seen and commented

UKCAB Business:

Next meeting: **01 May 2009**

Topic: Resistance re-visited