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Presentations are all available to download for the April 2011 meeting at:
http://www.ukcab.net/resources/presentations/
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<td>Dr Tristan Barber</td>
<td>Chelsea and Westminster Hospital</td>
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<tr>
<td>Dr Sam Nightingale</td>
<td>MRC Research Clinical Fellow</td>
<td>Liverpool</td>
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### Apologies:

John O’Callaghan-Williamson  
T-Cell  
London
# Programme:

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Introduction
The meeting was going look at how HIV affects the brain, an area with lots of questions and so far very few answers. HIV causes inflammation in other organs, so perhaps also in the brain.

HAART has changed the treatment of HIV so that many people living with HIV can now lead long and productive lives. However the brain is a very sensitive organ and the body keeps it protected from substances it does not recognise. As a result HIV drugs have difficulty entering the brain and are often pumped back out if they do enter. This means that the level of drugs in brain fluid can be as little as 1% of that in blood.

A lot of studies show that for different reasons these low levels may be enough – but do we need this from one, two or all three drugs? In some people HIV can be found in the brain despite it being undetectable in blood. Sometimes the reverse is true. Does this matter? Other studies looking at symptoms have shown that up to half of HIV positive people can have minor problems with thinking and memory, despite treatment.

The meeting hoped to discuss questions such as:
• What tests can I have for brain impairment?
• What can and can’t the doctor measure in the brain?
• Are there any tools to improve brain impairment?
• What drugs best penetrate the CSF?
• What studies are being done on HIV and the brain?
• How much virus gets to the brain in the cerebrospinal fluid (CSF); is this important and can it be measured?
• Is the choice of treatment likely to be important for everyone despite gender or ethnicity?

UKAB updates – the chair welcomed all and thanked the attendees for all arriving on time. Attendees were encouraged to ask questions around any jargon that maybe used during the meeting.

HIV and brain function
Dr Tristan Barber, Chelsea and Westminster Hospital

Dr Barber is a GUM/HIV doctor currently working at Chelsea and Westminster Hospital on a project looking at HIV and neurocognitive impairment. He has trained in HIV and sexual health at St Mary’s, Mortimer Market and Chelsea and Westminster.

Dr Barber’s presentation looked at when HIV could affect the brain and this could be during seroconversion, or long term infected but not on treatment, long term infected on treatment and old age. He described the types of memory failure which include non-HIV related memory failure such as Alzheimer’s and HIV Associated Neurocognitive Disorders (HAND) and described the symptoms associated with HAND.

Memory loss can be due to other causes such as:
• Sleep deprivation, thyroid disorders and vitamin B12 deficiency.
• Strokes or infections are associated with acute –onset memory changes.
• Worry about HIV diagnosis could lead to psychiatric problems
• Brain could be impaired before diagnosis

Diagnosis of HAND varies and remains broad as:
• Many patients have a psychiatric history.
• Substance abuse and/or withdrawal can cause brief cognitive changes that complicate the diagnosis.
• Co-infection with (hepatitis C) and its treatment can cause cognitive impairment in HIV-infected individuals.
• Some ARVs can bring out neuropsychiatric symptoms; such as efavirenz, which can cause vivid dreams soon after initiation.

Unfortunately, no single laboratory test can establish the diagnosis of HAND, though a combination of tests including neuropsychological evaluation, neuro-imaging studies, and CSF analysis may support or prove differently the other diagnoses.

The prevalence of HAND in the older population varies. Older people have been found to have symptoms related to depression, alcohol and drug abuse compared to the HIV negative controls.

Dr Barber showed that ART can improve brain impairment, although damaged brain may heal poorly. If the viral load in the blood is high, it is likely to be high in the CSF, it is therefore important to suppress the blood viral load. Low CD4 count could result in a damaged brain may heal poorly leading to poor brain function. The best measure for brain viral load is to measure the CSF viral load. This was proved in the data from the CHARTER cohort study.

The tests that can be done are:
  i. Assessments that take 30-60 minutes.
  ii. Neuropsychological evaluation could take up to half a day.
  iii. MRI to look at brain tissue.
  iv. Lumber puncture to check for viral load in the CSF.
  v. They are developing a 20-30 min test that could be done quickly in a clinic.

Tests at Chelsea and Westminster include the standard anxiety and depression questionnaires, the every day memory questionnaire and International HIV Dementia Scale. He concluded with data from BHIVA 2011 and show that brain problems are not as extreme for people who are virologically suppressed on treatment.

Discussion:

Q: Which people are getting problems whilst on treatment and what problems do they have?
A: If CD4 gets low, brain function could be affected.

Q: Is there a way to get round that; can nurses do the tests other than doctor?
A: In some clinics nurses can do the test through computer-based tests, etc. Research is looking and mild and moderate problems. It is difficult to work out what is HIV-related and not.

Comment: HAND has been diagnosed in some cases in people who are about 19-20 years who then turn out to test positive for HIV.

Q: In terms of everyday memory, how do you quantify remembering certain things like mobile numbers?
A: not a specific question, not precise question

Q: Will HAND get any better, not like in the 80’s, what can we look out for?
A: There is need to tease out what is HIV-related and age-related and whether Alzheimer’s occurs early in HIV. A few centres are looking into such studies of younger cohort below 50 years.

Comment: would be interesting if research groups could get in touch with the CAB and involve them in research. It would also be helpful if these studies could coordinate with each other.

A: They could and there are pros to this: different tests could pick up different things, cons: same tests could use the same format and we might miss certain things.

Q: I am concerned about children born with HIV who may not be on treatment for a long time; do they get tested for brain impairment?
A: There was study where the community was involved and data was presented a year later, focus on younger children who go for long period without treatment.

Q: Qs for anxiety – scoring
A: high scorers often have high anxiety

Comment: In the PIVOT study there is a sub-study on viral load in the CNS, participants underwent CNS tests and will be repeated annually so in a few years there will be data on monotherapy and triple therapy.
A: I would suggest having a neurocognitive group with patient representation.

Q: We use the MMC screening tool in Stranraer and diagnosed a few people under 65 could it be used in HIV clinics?
A: The MMC is not a good tool for diagnosing HAND.

Q: My diet is mainly to reduce cholesterol and lower blood pressure; does high blood pressure affect brain function?
A: High blood pressure has negative impact on brain function.

Q: How do you separate efavirenz side effects and HAND?
A: There are split answers on efavirenz: – patients stable on efavirenz do not need to switch, there is no evidence that switching makes a difference. However, those who switched reported feeling a lot better, not sure if its biological or psychological.

Q: How useful are MRI scans in diagnosing brain impairment?
A: They are not useful if there is no problem.

Dr Tristan’s full sides are available here.

Company pre-meeting
Ben Cromarty, North Yorkshire AIDS Action

Ben led the discussion by giving a background of Abbott’s share in HIV market and they only have one drug, lopinavir/r.

Agenda:
1. Abbot normally say that have nothing in the pipeline but now seem to suggest something coming through from pre-clinical trials on Hep C.
2. HCV – should question on the vile taste of ritonavir for children. In other meetings they say they maybe paediatric granules, but not sign of the 50mg tablet.
3. The meeting should also ask about the Department of Health’s change in the way the NHS buys drugs. They are looking at “value” of drugs, payment by results and we would like to know if Abbott contributed to that discussion and what their view is on this.
   b. Ritonavir dosing is important; it shuts down some liver enzymes so HIV stays in the body longer. They may be no need for so much ritonavir. What are they doing about producing a lower dose formulation of ritonavir?
4. Any new formulations of kaletra in tablet form?
5. Talk about London commission with a possible switch from kaletra.
6. Update on PROGRESS study.
7. As about their Diagnostics, a 4th generation tests picks up infection as early as 4 weeks vs Alere which picks up infection in 2 weeks. What percentage does their test pick up?

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**ARTs and minds: HIV, antiretroviral therapy and the mind**

*Dr Sam Nightingale, MRC Research Fellow*

Dr Sam Nightingale is a neurologist with an interest in brain infections. He is currently an MRC Clinical Research Fellow working in Liverpool with the HIV-Pharmacology Group and the Brain Infections Group. His research is looking at how antiretroviral drugs penetrate the brain, and what effect this has on the individual.

Dr Nightingale started by explaining the confusing terminologies around brain impairment and highlighted that even some web searches do get them wrong!

**Why is the brain affected by HIV?**

HIV enters the brain in early infection, and then the virus produces substances that are toxic to the brain cells. The body produces inflammation to try to attack the virus. The HIV-associated neural injury leads to brain impairment. Without ART this can lead to HIV dementia, which is now less common. However, milder impairment is common with symptoms such as memory problems, poor concentration, reading difficulties, slowness of thought, social withdrawal, depression which is associated with worse quality of life, reduced adherence and earlier death.

**ARTs penetration into the brain:**

As some antiretrovirals do not penetrate the CNS well, the brain is considered a separate “compartment” where HIV can hide. A CNS Penetration Effectiveness (CPE) chart showed the following ranking; the higher the score the better brain penetration:

- **4 (High):** zidovudine, nevirapine, indinavir/r
- **3 (Intermediate):** abacavir, stavudine, emtricitabine, efavirenz, delavirdine, fosamprenavir/r darunavir/r, indinavir, lopinavir/r maraviroc, raltegravir
- **2 (Low):** didasoninne, lamivudine, stavudine, etravirine, atazananvir, atazanavir/r, fosamprenavir
- **1 (Very low):** tenofovir, zalcitabine, nelfinavir, ritonavir, saquinavir, tripranavir, enfuvirtide
Detectable HIV in the spinal fluid
In one study HIV was detectable in the CSF of 10% of asymptomatic patients who had blood undetectable viral loads. This is because ARVs have variable penetration across the blood-brain barrier, suggesting that viral replication may continue in the CNS despite suppression in the blood. These patients differed significantly from those without detectable CSF viral load, in that they had:

- Higher CSF neopterin levels (a marker of inflammation)
- Longer exposure to ART
- A greater number of previous viral blips
- A greater likelihood of previous treatment interruption

No difference was seen in the CPE rank of regimens used by patients with detectable CSF viral load and those without.

UK research in this area:
Dr Nightingale is involved in the following studies with nine sites around the UK:

**Study A:** CNS penetration of antiretrovirals – the role of pharmacogenetic factors in variability.
This study is collecting CSF samples from HIV positive people. Samples are also collected through those already having a lumbar puncture for other reason, and a blood sample to determine DNA. This is to conduct genetic tests that will identify which drugs respond better to various ethnicities.

**Study B:** The CNS as a sanctuary site for HIV - it’s role in antiretroviral treatment failure:
The study is including participants who have had blips while on treatment, but go on to have undetectable viral load without changing treatment and without documented resistance. The study will look to see if there is more HIV in the CSF of people with treatment failure. Can HIV grow in the brain and spinal fluid where the drug levels are low? A lumbar puncture is necessary for this study.

Dr Nightingale also recommended further reading at: [www.braininfections.org](http://www.braininfections.org)

Discussion:

Q: Is the patient information online on [www.braininfections.org](http://www.braininfections.org) encrypted?
A: Yes it secure each patient will have a secure login.

Q: Are you looking at other HIV sanctuary sites?
A: Testis are a possible site, but have no studies at the moment, we are mainly relying on CSF through lumbar puncture.

Q: How do you persuade people to do lumbar puncture for research?
A: Lumbar puncture gets bad press because of side effects, but there is use of special needles that reduce post-lumbar headache.

Q: How do you measure drug levels on drugs that need protein binding, as the brain has no protein?
A: It is difficult to do and we estimate on the levels in the CSF.

Comment. The comment in your presentation on neurocognitive effects on treatment interruption is not helpful saying people got better cognitive impairment after coming off treatment.
Comment: Could you produce patient guides on lumbar puncture, as it is generally known to be horrible?

C: When you have two blips, you may change treatment but the viral load maybe normal when you have e for a lumbar puncture.

A: After spinal fluid is tested, it would be clear that they are detectable in the sanctuary sites.

Q: Do you have gender-specific questions especially for women, how does this relate in your studies?

A: We are looking at what factors affect what person, will get as many ethnic groups as we can with different genetic make up.

Q: Are you doing any research on children and young people with dementia?

A: The minimum age for this research is 16, so we are not looking at children. I am not aware of any trials going on with children.

Q: Are you involved in the lopinavir nano formulation study at Liverpool?

A: No.

Q: How do you control toxicity; is it the drug or the virus?

A: It is difficult to difficult to tease out; efavirenz is known to be neurotoxic.

Dr Nightingale’s presentation slides can be found here.

Company meeting with Abbot
Tayo Erogbogbo, Community Relations Manager and Dr Ansuya Naidoo, Medical Advisor

After introductions a minute’s silence was observed in memory of those who were and are unable to benefit from advances in HIV treatments.

Tayo Erogbogbo gave a brief introduction of Abbott, whose focus is also on mental health issues, peer support.

Dr Ansuya Naidoo, Medical Advisor

Dr Naidoo spoke about Abbott’s global fund for research on HIV. The fund was created to work with investigators around the world. There are four studies funded in the UK on TB, perspectives of long-term therapy, women and neurocognitive function. There is a global study to assess prevalence of a positive screen for anxiety, depression and neurocognitive function in people living with HIV. She also spoke on some of Abbott’s funded studies

Q: Could we have more information on neurocognitive study you are doing?

A: The study is comparing HIV treatment naïve vs HIV experienced patients and comparing the data.

PROGRESS study compared combinations of lopinavir/r and raltegravir vs lopinavir/r and truvada on ART-naïve adult patients. Data from the study was that that lopinavir/r generally both were well tolerated.

Q: What were the lipids like in PROGRESS?

A: There was no significant difference although lipid elevations were observed more frequently in the lopinavir/r and truvada group.
Novel studies:

- Lpv/r+3TC (dual therapy) to avoid NRTI toxicity, simplicity, cost, less safety monitoring needed, feasible in resource limited setting.
- HCV compound in development – interferon-containing regimen and interferon-free regimen (for those who can’t tolerate IFN)

Q&A

Q: Many pharmas are stepping away from HIV to doing other stuff. What is your commitment in the next years in the next 10yrs?
A: We have ongoing research and also working into Hep C and nothing in the HIV pipeline.
Q: What formulations do you have for children?
A: Alluvia in resource limited settings and we continue to try and have more drugs accessible in most affected areas.

Q: Will you ever have a 50mg formulation of ritonavir? The paediatric formulation tastes horrible, are you considering something better tasting for children?
A: Abbott is working on the taste of ritonavir, but there is nothing at the moment.

Q: There is a lot of emphasis is on medication to control HIV; is there any commitment towards a cure? A cure would be more cost effective.
A: That is a fair assessment; we are working with investigators on eradicating the virus in sanctuary sites and hopefully lead to complete eradication of the virus in the body such as the nano technology.

Q: What have you learnt from research from Africa and how that benefit Africans in the UK?
A: There are exciting learnings e.g. social issues such as not breastfeeding, also observed that kidney disease is higher in the African population, so we increase monitoring for Africans in the UK and this has been added to the treatment guidelines.

Q: Have you been involved in the valued-based pricing, what is the cheapest drug available for the best outcome?
A: It’s the biggest issue facing pharmas right now; our consideration is what the drug appropriate for individual patients.

Q: How are you going to counter the value-based pricing?
A: We need to think about what is the best option for patients; we submitted a response to the consultation, which is not publicly available. We believe it should all be patient-centred.

Q: Are you going to bring new drugs, our concern is that you may go away from HIV and do something new? Can you sustain this in 5-10 yrs?
A: I can’t answer but we are not planning to pull out of HIV. Lopinavir/r is used worldwide. We are actively looking/thinking for new combinations?
Changes to HIV drug prescribing in London and what implications this could have for the rest of the UK
Led by Silvia Petretti and Robert Fieldhouse

The Summary of ARV prescribing guidelines in London slides had been circulated for discussion at the meeting. The lead clinicians met and agreed on:

- Clinical guidelines for prescribing kivexa as first choice in treatment-naive patients and for atazanavir as the PI of choice with potential for switching existing patients.
- Agree process to achieve equitable approach across all London providers to implementing agreed changes in prescribing priorities.
- From 1 April 2011: New contract will start and will run for 2 years.

A meeting was called in Bournemouth with Claire Foreman to discuss community concerns, as the UKCAB do not feel we have been adequately consulted on these changes. The community would emphasised it would be good to know when the tender process began and who sits on the board that made these decisions? There is no scientific evidence on the benefit of making kivexa first line treatment or switching patients already on truvada. The community feels this is all cost-based and not patient based. Claire did not commit but said she would come back with answers, evidence and more transparency. Robert Fieldhouse is writing the full minutes of that meeting.

There should be a strong voice from the community saying that prescribing should be according to patients needs, efficacy and not cost!

The is a PPE meeting on 19 April 2011, details to be circulated on the CAB forum and anyone can attend, but there is need to advise them you are coming.

The community should involve London mayors and MPs in lobbying for the pan-London clinics, Michael Platt offered to take lead in getting to the London mayor.

Can the CAB link into the local government HIV network?

UKCAB AOB:
UN Special Session on AIDS meeting in June – needs a positive person living with HIV on the UK delegation

The MRC-CTU is moving and will not be able to host community meetings. The venue for the next meeting is being sought and will be announced in due course.

Next meeting:
Date: 08 July 2011
Topic: Hep C and transplants (liver and kidney)