UK CAB
HIV treatment advocates network

CAB 37: Treatment as prevention
04 February 2011

Contents:

Presentations are all available to download for the February 2011 meeting at:
http://www.ukcab.net/xxx

List of attendees

	Name	Organisation	Destination
1	Angelina Namiba	Positively UK	London
2	Angeline Marang	HIV i-Base	London
3	Badru Male	CHAT	London
4	Ben Cromaty	North Yorkshire AIDS Action	Yorkshire
5	Charlie Walker	HIV i-Base	London
6	Damian Kelly	George House Trust	Manchester
7	Fabiola Bayavuge	Black Health Agency	Manchester
8	Gemma Spink	AVERT	Horsham
9	Gertrude Wafula	Black Health Agency	Manchester
10	Godwyns Onwucheka	Personal	London
11	Gus Cairns	NAM	London
12	Jeff Ukiri	Personal	Manchester
13	Memory Sachikonye	UKCAB	London
14	Michael Marr	Waverley Care	Edinburgh
15	Munya Mudarikiri	Body and Soul/CHIVA	Manchester
16	Roger Pebody	NAM	London
17	Sarah Radcliffe	National AIDS Trust	London
18	Simon Collins	HIV i-Base	London
19	Tsepo Young	NHS Dumfries and Galloway	Stranraer
20	Tsitsi Nyamapfene	Brent Community Services	London
21	Winnie Ssanyu Sseruma	HIV i-Base	London
Speakers			
	Dr Colette Smith	UCL Medical School – Royal Free Hospital	London
	Dr Steve Taylor	Heart of England NHS Trust	Birmingham

Apologies:

Brian West
Andrew Chuba
Eneya Chuba
Maurice Hebert
Paul Clift

Programme

Chair: Michael Marr	
09:30 - 10:00	**Registration, refreshments and expenses**
10:00 - 10:05	**Welcome and UKCAB Updates**
10:05 – 10.30	**Pre-Meeting for Gilead**
10:30 - 11:30	**iPrEX Trial design; statistical aspect of the results relating to the adherence data** – Dr Colette Smith, Royal Free Hospital, London
11:30 - 11:40	**Break**
11:40 - 12:40	**Science behind PrEP/Pharmacology Training; complexity of how drugs are absorbed and measured in different body compartments, and particularly for PrEP –** Dr Steve Taylor, Heart of England NHS Trust, Birmingham
12:40 - 14:00	**Lunch**
Chair: Badru Male	**Timekeeper:** Gertrude Anyango Wafula
14:00 - 15:30	**Company meeting: Gilead**
15.30 - 15.35	**Break**
15:35 – 16:00	**UKCAB AOB: PIVOT Trial: Possible Analyses of Collected Data –** Ben Cromaty
16.00	Close

About the speakers:

Dr Colette Smith is a statistician and epidemiologist working for UCL Medical School at the Royal Free Hospital, London, UK. Her work is primarily involved in analyzing routinely-collected data and data from randomized controlled trials. Her HIV interests include investigating the impact of antiretroviral therapy on the occurrence non-AIDS events, long-term immunological and virological response to treatment and outcomes of individuals co-infected with hepatitis and tuberculosis.

Dr Steve Taylor is a lead consultant Physician - HIV and Sexually Transmitted Infections at the Heart of England NHS Trust in Birmingham. His PhD thesis entitled 'The Sexual Transmission of HIV' focused on HIV in the male genital tract and the impact of sexually transmitted infections and antiretroviral therapy (ART). It also covered the pharmacokinetics and pharmacodynamics of ART in the male genital tract and the evolution and sexual transmission of drug resistant HIV. He has presented and published widely in these research areas and has been an invited speaker at several International HIV conferences.

Pre-meeting for Gilead - Michael Marr

Michael led the pre-meeting. He listed all the drugs currently in use by Gilead and the meeting set the following agenda:

1. Safety of elvitrgravir, the pipeline INI.
2. Update on GS9350 – the pipeline booster agent to be used as replacement for ritonavir.
3. Update on the QUAD – a new four-in-one once daily pill, and also ask if they have any idea on pricing.
4. Data on tenofovir on bone health. Is this related to age, and how this is being monitored in clinics? There are studies that have revealed a strong correlation between loss of bone density in HIV positive individuals.
5. Is Gilead involved in monitoring long-term health?
6. DAD study now looking at renal – what are they doing?
7. Gilead's position the patent-poll for middle-income countries.

The meeting discussed the issue of Gilead are trying to get the community to campaign for atripla; 1 vs 2 pills. With the funding cuts coming in the near future, the discussion was to determine whether taking one pill as opposed to two would have an effect on adherence. The general consensus was that an extra pill once day would not affect adherence, but if there are more pills more than once a day, that maybe a problem for other people. The community would like to protect their NHS services and are happy to take two pills once a day.

---

iPrEX Trial design; statistical aspect of the results relating to the adherence data – Dr Colette Smith

Dr Colette Smith is a statistician and epidemiologist working for UCL Medical School at the Royal Free Hospital, London, UK. Her work is primarily involved in analyzing routinely-collected data and data from randomized controlled trials. Her HIV interests include investigating the impact of antiretroviral therapy on the occurrence non-AIDS events, long-term immunological and virological response to treatment and outcomes of individuals co-infected with hepatitis and tuberculosis.

About iPrEX:
This is a study to demonstrate the efficacy of an HIV prevention strategy involving nearly 2,500 HIV-negative, gay men, transgender women, and other men who have sex with men who are considered to be at high risk of acquiring HIV. The study took place in 11 sites and was a randomized, placebo controlled, with half of the study participants given once-daily truvada and the other half on placebo. The study results proved the concept of pre-exposure prophylaxis (PrEP) - taking antiretroviral drugs before exposure to HIV. The use of truvada led to significant lower rate of new HIV transmissions compared to the placebo.

Dr Smith's presentation was looking at adherence on the participants who became HIV positive during the study. Study participants were asked to take the drug once daily throughout the study. Adherence was tracked through self-reporting through computer-assisted self-administered interviews (CASI), interviewer-administered interviews, pill counts and measurements of drug concentrations in blood and hair.

The main results at the end of the study showed that there were new infections amongst the participants in the placebo arm. Adherence was varied in this arm, a quarter reported being 88% adherent, one-fifth did not know how many pills they had missed and one-fifth were not taking the study drug. The interesting fact in the result was that more half of the participants had reported taking all the doses.

The meeting discussed issues around adherence:

Q: Why are there still infections?
A: With self-reporting there is a possibility of over estimating drug levels in those who became positive. Those who became HIV-positive during the study were less likely to have detectable drug levels in their blood. Similar results were obtained from hair samples.

Q: Is there a similar study to iPrEX on heterosexuals?
A: There is a study going on in Thailand and another from southern Africa that will report in 2013.

Q: Would they use the same drugs in heterosexuals?
A: There was no difference in animal studies. CDC has interim guidelines to use truvada as long as they follow study design in high-risk population.

Comment: Taking truvada shortly before sex as PrEP will not work.

Q: What drug is used for PrEP for timed-conception?
A: Taking truvada everyday you get PrEP and PEP and should therefore work for timed-conception. In the iPrEX trial, sensitivity was two weeks.

Comment: In the roll over study participants will be more encouraged to take the drug knowing it works.

Q: Did they look at side effects – bone and kidney?
A: Very few people had blood results of kidney problems; there was more nausea for participants on truvada.

Q: Is there any known interaction of oral contraceptive and ART?
A: Some PIs do have interactions – nevirapine, lopinavir,nelfinavir and ritonavir - have demonstrated signifanct interactions.

Comment: Women are adherent to oral contraceptives as they do not want to get pregnant. If ART came in blister packs with days of the week like oral contraceptives that would help with adherence as you would remember whether you had taken your meds or not.

Members were informed they could ask for a dosette box from their pharmacy to aid adherence.

From the study, people are saying they will use prep intermittently. This could be similar as in the FOTO study (five days on two days off meds) where study participants took a weekend break from ART and had no viral rebound.

Q: Why don't people adhere?
A: Living conditions and social circumstances contribute to this.

Q: Interesting to know drug levels can be measured in hair samples. Do HIV drugs make your hair grow?
A: There was a study that reported hair loss after 3TC?

Q: Is a hair sample cheaper to test for drug levels vs blood sample?
A: Hair is cheaper.

Dr Smith's presentation can be found here.

The Partner study: http://www.partnerstudy.eu/
The Partner study is enrolling couples where one partner is HIV positive and the other is HIV negative. This new study is looking at the risks of HIV transmission when someone is taking effective HIV treatment. Community members who are eligible were encouraged to enrol so proper estimates on transmission can be determined.

Drug penetration into genital tract: Implications for sexual transmission - Dr Steve Taylor

Dr Steve Taylor is a lead consultant Physician - HIV and Sexually Transmitted Infections at the Heart of England NHS Trust in Birmingham. His PhD thesis entitled 'The Sexual Transmission of HIV' focused on HIV in the male genital tract and the impact of sexually transmitted infections and antiretroviral therapy (ART). It also covered the pharmacokinetics and pharmacodynamics of ART in the male genital tract and the evolution and sexual transmission of drug resistant HIV. He has presented and published widely in these research areas and has been an invited speaker at several International HIV conferences.

He started off by introducing the Saving Lives programme at his hospital. Saving lives campaign was a response to a clear local issue: there was no agreed procedure for identifying and referring patients who might need an HIV test. The campaign thus initially centred on how best to provide both clinicians, healthcare professionals and the public with the information they needed to improve understanding, and HIV awareness in the region, with the ultimate aim of decreasing the numbers of people with undiagnosed HIV in the local community. For more information about the campaign visit:
http://www.savinglivesuk.com/

Dr Taylor's presentation was on how different HIV drugs penetrate in the genital tract (GT), by gender. Measuring absolute drug levels in the GT is complicated. Some drugs are rapidly absorbed in the blood but might take longer to reach higher concentrations in the GT. The GT/blood plasma (BP) ration changes depending on the time the drug is taken.

Recent studies have confirmed that penetration of antiretroviral agents into the male and female GTs are both drug and sex specific. Concentrations achieved varied considerably by class of drug studied, the sampling techniques used and the times samples are obtained.

In men:
High GT concentrations:
- NRTIs – 3TC, zidovudine
- INI - raltegravir

Low GT concentrations:
- PIs – darunavir, lopinavir saquinavir, rinotovair, amprenavir
- NNRTIs - efavirenz, nevariparine and delavirdune
- CCR5 – maraviroc

In women:
- NRTIs concentrations in the GT varied:
    - 3TC, zidovudine and emitricitabine - had high GT concentrations.
    - Truvada, ddI, abacavir and d4T had low GT concentrations
- INI – maraviroc had high GT concentrations

Low GT concentrations:
- PIs – ritonavir, lopinavir and atazanavir
- NNRTIs – efavirenz

From these tiny data sets, there appears to be several patterns of drug penetration into the male and female genital tract. Genital tract penetration of drugs and control of viral replication in the genital tract is important in the prevention of sexual transmission of HIV. The NRTIs generally penetrate well into male and female genital tracts. NNRTIs appear to penetrate into female genital tracts but PI penetration is more inconsistent possibly related to plasma protein binding.

Q: In microbicide development, will there be different ones for men and women?

Due to time constraints the discussion was continued during lunch, all slides are available here.

Company meeting: Gilead

After introductions, the meeting observed a minute silence in memory of those who died and could not benefit from the HIV treatment that is now available and also to David Kato, the Ugandan gay rights activist who was murdered in Uganda on 27 January 2011.

Dr Romina Quercia from Gilead presented on TDF safety, pipeline ARVs and pipeline HCV.

Tenofovir (TDF) safety:
Dr Romina Quercia presented data fromthe 934 study on TDF's long-term efficacy and safety, in particular the occurrence of kidney and bone problems, which have been attributed to TDF in some previous studies. In the 934, naïve participants were randomly assigned to receive truvada or combivir both in combination with efavirenz. After 144 weeks, 286 patients from both arms switched to atripla and continued follow-up. Atripla was well tolerated and maintained viral suppression through 48 weeks. Participants on combivir and efavirenz for 3 years, switching to atripla did not significantly improve limb fat after 48 weeks.

On viral suppression, TDF long-term efficacy safety date for 10 years showed that 64% remain undetectable.

There was reduced renal function in the first two years which then stabilised. The study was on a 100 patients; two developed an increased creatinine levels and discontinued the study.

Bone mineral density (BMD): there was a reduction of -2 and -3 of the hip and spine, although small, but it is a statistically significant decline. Larger studies with longer follow-up are needed to determine these changes.

Comments:
- We need to know if the researchers looked at any age-related BMD.

- Toxicity – when asked on grade of toxicity in the 934 trial, Dr Quercia did not have the details and would send these after later.
- We need to know if these are results for people in the study who could tolerate tenofovir?
- The figure in the presentation did not have specific ranges and it would have been helpful to have the ranges rather than just a line.

Discussion on adherence – do less pills improve adherence and quality of life (QoL) in studies? Results from a study on one vs two pills had a confidence interval of 1.4-25.8 (too wide), so there is no difference at all.

Q: How do you measure QoL?
A: Participants fill out questionnaires that evaluate different aspects of a their daily life.

Q: Does pill count account for the 85% adherence on ECHO and THRIVE studies?
A: It was self reported adherence.

Gilead Pipeline drugs:

Phase III
- Truvada/TMC 278 - has shown activity against NNRTI-resistant HIV.
- Elvitegravir (INI) once -daily Quad (elvitegravir/FTC/tenofovir/cobicistat)
- Cobicistat (formerly GS 9350) (PK enhancer)

Phase I
- GS 7340 (NRTI) - targeting the lymphatic system, lowers plasmatic concentration and has long half-life.

Hep C – Phase II
- GS 9190, GS 9256 - two oral anti Hepatitis C virus (HCV) drugs, for 28 days with and without ribavirin and with pegylated interferon in adults with chronic HCV.
- GS 9451 (PI)

Phase I
- GS 5885
- GS 9620 (also for hep B)
- GS 6620

Discussion:

- Comment: Anti-acid with rilpivirine makes it useless, therefore people need to know need to know what these foods to avoid.
- Resistance – patients who fail on rilvpirine, lose the use efavirenz, it is important for patients to know which drug to start with. In general if fail on an NNRTI you should go to another class. 2nd generation NNRTIs can work if you fail on 1st line NNRTI.

AOB – Ben Cromarty

House of Lords – call for evidence, need to look particularly on the treatment site, thoughts and comments to be submitted before 18 February to Paul Clift via the UKCAB forum.

PIVOT study

The aim of PIVOT is to investigate the effects of taking only one type of anti-HIV drug (protease inhibitors), on disease progression and death in people with HIV.

The trial will run for 5 years, looking at any possible long-term impacts of monotherapy, particularly looking at the possible loss of future drug options due to development of resistance. The trial steering committee (TSC) would welcome suggestions from the community with regard to what studies might usefully be done.
Some suggestions are:

- Descriptive analysis of pre-baseline ART history and reasons for switching drugs.
- Peripheral neuropathy: prevalence; relationship with demographic factors, disease factors and drug exposure.
- Neurocognitive function: assessment of the sensitivity of the different methods for detecting impairment; reliability; issues in performing tests.
- Neurocognitive function: prevalence of impairment; relationship with demographic factors, disease factors and individual drug exposure.
- Quality of Life: relationship with demographic factors, disease factors and individual drug exposure.
- Cardiovascular risk: descriptive analysis and analysis of relationship with demographic factors.

Comments and discussions can be posted to Ben on the UKCAB forum:
http://www.ukcab.net/forum/index.php?topic=1094.0

More information about the PIVOT study can be found at:
http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=55

UKCAB re-designed website was shown to the meeting by Memory who also urged members to send in news items from their areas/region. The website is at:
http://www.ukcab.net/

Next meeting: 15 April 2011
Topic: HIV and the brain