

# UK CAB

## HIV treatment advocates network

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### CAB 40: Gender and HIV research 21 October 2011

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Presentations are all available to download for the October meeting at:  
<http://www.ukcab.net/meetings/presentations/>

## Members attending:

No	Name	Organisation	Destination
1	Adebisi Alimi	HIV i-Base	London
2	Albert Biete	Personal	Derby
3	Andrew Shamboko	Personal	Liverpool
4	Angelina Namiba	HIV i-Base	London
5	Badru Male	CHAT	London
6	Ben Cromarty	NYAA	Yorkshire
7	Brian West	Waverley Care	Edinburgh
8	Carmen Tarrades	ICW Global	London
9	Claudia Stoicescu	IHRA	London
10	Damian Kelly	George House Trust	Manchester
11	David Rowlands	Baseline Magazine	Birmingham
12	Emma Hudson	The Brunswick Centre	Halifax
13	Emma Rezel	Personal	London
14	Eunice Sinyemu	AHPN	London
15	Fabiola Bayavuge	The Black Health Agency	Manchester
16	Gertrude Anyango-Wafula	The Black Health Agency	Manchester
17	Gus Cairns	NAM	London
18	Jet Lengalenga	Personal	London
19	Li Marhaban	HIV i-Base	London
20	Mark Platt	Personal	London
21	Memory Sachikonye	UKCAB	London
22	Michael Marr	Waverley Care	Edinburgh
23	Munasimenda Kanyama	Mildmay Hospital	Braintree
24	Paul Clift	King's Hosp/UKCAB	London
25	Quinet Akanoh	THT London	London
26	Robert Fieldhouse	Baseline Magazine	Birmingham
27	Robert James	Brighton Patient Rep	Brighton
28	Roger Pebody	NAM	London
29	Silvia Petretti	Positively UK	London
30	Steven Akenhurst	NAT	London
31	Stewart Murau	George House Trust	Manchester

## Programme:

<b>Chair:</b> Michael Marr	
09:30 – 09:45	Registration, refreshments and expenses
09:45 – 10:00	Welcome, introductions, UKCAB updates, Company pre-meeting
10:00 – 10:30	<b>Gender and HIV research: history and overview</b> – Angelina Namiba, HIV i-Base
10:30 – 11.30	<b>Outcomes in HIV positive women</b> – Lucy Campbell, Kings College Hospital
11:30 - 11:40	<b>Break</b>
11:40 – 12:40	<b>The XX factor – women and HIV</b> – Prof. Jane Anderson, Homerton University Hospital
12:40 - 14:00	<b>Lunch</b>
<b>Chair:</b> Brian West	
14:00 - 15:30	<b>Company meeting: BMS</b>
15.30 - 15.35	<b>Break</b>
15:35 – 16:00	<b>London HIV drug prescribing update and survey</b> – Mark Platt <b>UKCAB AOB</b>
16.00	Close

### About the speakers:

**Angelina Namiba** is a trainee treatment advocate at HIV i-Base and has over 13 years' experience of working in the HIV sector. She has worked on initiatives ranging from providing one-to-one support to people living with HIV; managing service provision to facilitating, promoting and advocating for the involvement of women living with HIV in forming and informing local and national strategy and policy. As a woman living with HIV for more than a decade, Angelina is passionate about advocating for the sexual health and reproductive rights of women living with HIV. From 2010 – 2011 she lead on the planning, development and delivery of the pilot project *From Pregnancy to Baby and Beyond*; aimed at developing a sustainable model of education, information, emotional and practical support, for women living with HIV through ante to post natal care.

**Lucy Campbell** is a Research Associate/Research Manager at Kings College London/Kings College Hospital. Her background is epidemiology and her job is a mixture of epidemiological studies focusing mainly on non-infectious co-morbidity in HIV as well as managing an ongoing programme of research. Her focus is mainly on observational research and has become aware that much of the research in HIV in the developed world revolves around cohorts with a male majority. Kings has a cohort of almost 50% women, which raises many questions and methodological challenges in analysing this data. She is very interested in understanding more about the generalisability of this published data fundamentally leading to a better understanding of our clinical population.

**Professor Jane Anderson** is a consultant physician, director of the centre for the study of sexual health and HIV and honorary senior lecturer at Barts and The London. She has a special interest in HIV treatment and care, HIV in women and families, management of HIV in pregnancy, psychosocial aspects of HIV care and care of migrant and ethnic minority communities with HIV. She is also the research lead for HIV and STI. She is the current chair of BHIVA.

## Introduction

Historically, women's health issues in conjunction with HIV research have not been thoroughly researched with only about 20% of women taking part in clinical trials. Women and men's bodies are different, and their reactions to medications can be different too. Better representation of women in clinical trials is essential for generating accurate information on the efficacy and safety of ARVs and, ultimately, guiding treatment decisions. More information is needed on specific drug doses for women, how infections and gynaecological conditions affect HIV-positive women, and what side effects are likely to affect women.

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## Gender and HIV research: history and overview

Angelina Namiba, HIV i-Base

Angelina's presentation was a brief overview around women's involvement in clinical trials and looked at some of the areas where there are differences linked to sex and gender. The numbers of women taking ARVs is increasing and that majority of women do well on ARVs. However, less is still known about women because there are difficulties in enrolling women in clinical trials as they are likely to get pregnant and the trial drugs could potentially harm the unborn baby. Pregnancy is an automatic exclusion factor for clinical trials in women.

1993 regulations changed to include more women but progress has been slow. The GRACE study is the largest study to date in that recruited treatment-experienced adult women with HIV-1 to examine gender and race differences in response to darunavir co-administered with ritonavir as part of combination therapy.

A show of hands in the meeting showed that most people had not taken part in clinical trials. Reasons given were not very different from the same reasons in lack of representation of women in clinical trials that include:

- Worry about safety of the trial drugs
- Distrust of clinical trials
- Stigma surrounding clinical trials and being associated as HIV positive
- Lack of support
- Lack of information about studies
- Lack of child care and transport costs to participate

On gender balance in clinical trials men tend to put off treatment but raises the question why women more likely to report health problems and not take part in clinical trials?

In the trials that have been conducted, have found differences linked to gender: Women have lower body weight, less average blood plasma compared to men and this has an effect on pharmacokinetics (the action of drugs in the body over a period of time, including the processes of absorption). The effect of these differences on ART efficacy and safety in women remains unclear. Ancestral history or pharmacogenomics (the study of the interaction of an individual's genetic makeup and response to a drug) has shown differences; Africans and Asians have higher EFV concentrations and lower ABC sensitivity.

ARV side effects have been reported more in women on PIs than men with more lipodystrophy in back and abdominal regions.

Menstruation, sex hormones, menopause and oral contraception – ARVs have no impact on periods. Atazanavir and efavirenz increase plasma concentration of some oral contraceptives and lopinavir, nelfinavir, nevirapine and ritonavir decrease concentration of oral contraceptives.

There isn't much data looking into bone mineral density as not enough women fit these criteria. A new group of ageing women is emerging and there have not been a lot of studies around menopause and as such more studies need to be carried out looking into this area.

Fertility and pregnancy – PI concentrations get reduced during pregnancy and not clear if reduced levels have any clinical effect. American guidelines recommend increase lopinavir in 3<sup>rd</sup> trimester while European guidelines don't, however TDM sometimes recommended.

Efavirenz is not recommended in the first trimester as it is known to cause birth defects, but some women can continue if fall pregnant while on it. There is only one study in monkeys only ever done with efavirenz, so there is no way of telling whether there is any greater risk than with other ARVs or indeed with the general pregnant population. EFV is classified as class D by the ARV pregnancy register, there is controversy as the study in monkeys was based on not very strong data without a denominator. The pregnancy register classes for ARVs are:

A	Adequate well-controlled studies of pregnant women fail to demonstrate risk.
B	Animal reproduction studies fail to demonstrate risk to foetus; adequate but well controlled studies of PG women not conducted.
C	Safety in human pregnancy not determined; animal studies positive for foetal safety or not conducted – should not be used unless potential benefit outweighs potential risk to foetus.
D	Positive evidence of human foetus risk based on adverse reaction data from investigational or marketing experience- potential benefits of drug might be acceptable despite its potential risks.
X	Studies among animals or reports of Adverse reactions have indicated risk associated with use for pregnant women clearly outweighs any possible benefit.

Social issues and adherence - women have a caring role and one study [Stein et al] of HIV positive mothers showed that as caregivers, women attach less priority to own healthcare needs and affects adherence as well as:

- Higher levels of parenting stress were associated with poor attendance at medical appointments.
- Adherence increased as the number of positive people living in the home decreased
- Women are 1.6 more times less likely to delay seeking HIV care than men and that having a child in the household was associated with not seeking adequate health- care.
- Alcohol and drug use, mental health issues also contribute to poor adherence.

Angelina concluded by emphasising the need for better representation of women in clinical trials and more studies on:

- ARV metabolism and adverse events
- Role of safety of new ARVs in pregnancy
- Global advocacy for increased access to treatment and fertility rights
- Provision of adequate social support

## **HIV research and gender**

Lucy Campbell, King's College Hospital, London

Lucy's presentation was on myocardial infarction (MI) and late presentation data from King's Hospital. She reiterated that men and women are different– on many levels, the most obvious are reproductive health, sexual health. In HIV studies there are other reported biological differences, pharmacogenetics/kinetics so the way drugs are metabolised is different.

There have been reports of different survival rates, different clinical progression, CD4 and adherence. There are other non-HIV health-related differences such as CVD risk and general reluctance of many to seek help; in a focus group of women, the barriers to care were identified as:

- Lack of knowledge on the part of health care providers
- Fear of negative treatment
- Insensitivity of health care providers
- Fear by providers, lack of patient education
- Lack of confidentiality, lack of honesty, and
- Blaming the victim.

These barriers have the potential impact on women's willingness to accept or continue treatment for HIV.

At King's Hospital the cohort of is made up of almost 50% women and an observational research showed that much of the research in HIV in the developed world revolves around cohorts with a male majority, which raises many questions and methodological challenges in analysing this data. The data on MI at Kings had 79% male population in the study.

Late presentation in the UK is estimate at 49% and is the most common cause for HIV-related deaths. At Kings, 59% of patients are late presenters while 35% will have a CD4 of less 200, women make up 37% of this group. Gender in HIV remains a complex question and differs by population. Data from observational studies is therefore difficult to interpret, it is important to carefully design studies to include women.

Discussion:

**Q: Are Africans still the worst at late presentation?**

A: Africans are not very different from other communities, but Caribbean men are poor at engaging in care.

**Q: From your data, I would like to see pregnant and non-pregnant figures. Is there any data on women presenting before pregnancy?**

A: Most women diagnosed during pregnancy and may disappear and then re-appear when pregnant. The experience of antenatal screening indicates that the majority of women accept HIV screening if it is offered as part of a package of care.

**Q: Do you go into detail to explore issues of late presentation?**

A: We only have routinely collected data; this needs more research.

**Comment: Could it be that some women could present early via GPs and that information is not being picked up resulting in missed diagnosis? There is need to encourage GPs to offer routine HIV testing.**

**Comment: In North Yorkshire, there is still a state of HIV denial in men thus increasing numbers of older people being testing positive, including for STIs.**

**Comment: IVDU are less likely to present late, they are offered HIV tests at clinics. Women however are better at using primary care.**

Q: Is there any relation between immigration status and late presentation?

A: Not really, but migrants who have been here a long time may think they have a lower risk compared to being in their home country.

**Comment: In some clinics women are being offered HIV testing during their colposcopy procedure. The aim is to reduce the time between acquisition and diagnosis of HIV by encouraging testing in settings where patients present with indicator diseases. Benefits of earlier HIV diagnosis include improved survival, prevention of onward transmission, and optimisation of maternal health when planning pregnancy. There is evidence that HIV reduces the effectiveness of standard treatment for cervical intraepithelial neoplasia (CIN) grade 2 or above and cervical cancer.**

**Comment: Could the UKCAB have a topic on designing studies? It would be an interesting discussion in Stiges on Hep C new trials. Since there is little data on pregnancy, there is need to collect some cohort data to give an idea. The meeting suggested persuading drug companies to try drugs on pregnant women. They could also capture clinical data on drugs pregnant women are taking and looking at outcomes.**

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### **The XX Factor: Women and HIV**

Jane Anderson, Homerton University Hospital

"Not treating women properly is bad news for everyone" was Jane's opening statement on treating women with HIV. Her presentation gave more detail of the issues raised in the overview by Angelina Namiba earlier.

She introduced the [SHE](#) programme whose aim is to build *Strong, HIV positive, Empowered* women through peer support sessions facilitated by women living with HIV. Held in peer support groups, the programme vision is to provide opportunities for women and girls to share experiences and ideas about living with HIV, offer helpful HIV information, and to provide empowerment to women.

Prenatal testing for women unless they specifically decline is increasingly recommended in most countries across Europe but some countries still do not offer it. She also spoke about barriers to HIV testing and a survey in Emergency Units and Acute care units within the UK showed that the HCP were not equipped and trained to answer questions and address patients concerns when they offer an HIV test.

There is equivalent efficacy between sexes in RCTs but the numbers are small with substantial variability within the data. There are ARV tolerability differences and effectiveness women are more likely to than men to discontinue treatment than men for reasons other than virological failure. Need to find out why, adverse events?

Currently the problem in addressing women's issues in HIV research is due to lack of women-specific data, and not enough women are enrolled in clinical trials. There is also lack of sex based analysis from current data with men are predominate observational and cohort studies and the use of estimates of male data to fit female population.

As mentioned in the overview section earlier in this report, women were more likely than men to discontinue treatment for other reasons than virological failure. Social and adherence issues still need to be addressed.

**Comment: Treatment as prevention in sero-different relationships HIV positive women feel they have a lot of responsibility in negotiating safe sex. Men may have multiple partners, plus there is fear of STIs.**

The FemPrEP study showed low genital tract (GT) of Tenofovir, further studies are required to look at other drugs with a higher GT penetration.

Conception and PMTCT:

Efavirenz data on foetal malformation: analysis of larger datasets of women and infants exposed to efavirenz in pregnancy shows no significant difference in the rate of birth defects compared to the general population. Birth defects are most likely to occur as a result of drug exposure during the first three months of pregnancy. The question is whether women are being denied a good drug due to fears? BMS said that they will leave EFV prescribing to the physician and this varies from country to country.

AZT is licensed for use in pregnancy, it is important to have a pre-conception discussion with doctor. AZT monotherapy is used to reduce perinatal HIV transmission in women with low viral loads. There are few data on the risk of drug resistance in this select cohort of women.

Breastfeeding: effective ARV therapy reduces HIV transmission to the infant. There are studies in resource-limited settings but the UK advice is still no breastfeeding for women with HIV.

**Q: What do you tell the woman who has been on efavirenz who wants to become pregnant? She won't want to stay on efavirenz if there is even the slightest risk it might harm her baby.**

*A: Most want to switch to nevirapine if it is safe to do.*

**Q: How do African women living with HIV access treatment information?**

*A: They take advice from the medical team and then check it out on the Internet.*

UK pregnancy guidelines are currently being re-written.

She summed up her presentation by saying:

- PMTCT is now shifting to give greater consideration of the women's wellbeing.
- ART as prevention is an important step forward, but studies with PrEP oral microbicides may be more effective.
- There is still not much difference in efficacy of ART between men and women, but effectiveness maybe affected adherence, toxicity, discontinuation and other social/cultural issues.

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## **Company meeting – Bristol Meyers Squibb (BMS)**

After introductions and a minute silence, Catherine Howland introduced Dr Nick Adomakoh who presented on:

### **Studies update:**

ATZ monotherapy ACTG 5201

This was a small study in Spain with 36 HIV-positive participants who an undetectable viral load for at least 48 weeks on a first ART regimen consisting PI plus two NRTIs. At week 24 after discontinuation of NRTIs, 91% of patients maintained an undetectable viral load - good adherence data (less pills). Three patients experienced virological failure, at 12, 14, and 20 weeks after NRTI discontinuation. There were no PI-resistance mutations in any of these three individuals. Two of these patients had no measurable atazanavir in their plasma samples at the time of virological failure suggesting that poor adherence may have contributed to virological failure. The third patient did have detectable atazanavir in his blood at each visit, and achieved re-suppression to below 50 copies/ml while remaining on boosted atazanavir monotherapy. No participants discontinued therapy following treatment simplification due to adverse events. Large, randomized trials needed to better define efficacy and safety of this approach.

## MODAT

A non-inferiority monotherapy study on the efficacy of atazanavir/ritonavir (ATV/r) vs ATV/r - based HAART. The aim of the present study is to demonstrate with a randomized trial, that, in carefully selected patients, ATV/r is an attractive option for a monotherapy strategy.

**Comment: The study was based in Italy and demographics of participants are not available. The PIVOT study did not allow ATV/r as monotherapy as it might not be as potent as conventional ART:**

<http://www.ncbi.nlm.nih.gov/pubmed/17159658>

## ACTG 5224

A study a sub-study of the larger ACTG trial 5202 that focused on changes after two years in bones and limb fat when comparing different regimens. The regimens with Truvada or Kivexa increased visceral abdominal fat. It concluded that all regimens seemed to have been associated with accelerated bone loss at the onset, but bone density became stable after the first year. Truvada was linked to greater loss of bone density in the hip and spine than Kivexa. Use of ATV/r was linked to greater loss of bone density in the spine compared to efavirenz. Regimens containing either Kivexa or Truvada had increased limb and trunk fat. Use of ATV/r resulted in a greater increase in limb fat than efavirenz. Fat wasting occurred in about 16% of participants and did not differ by study regimen.

## PRINCE study

The purpose of this study is to see if atazanavir granules combined with ritonavir are safe and well-tolerated and produced appropriate drug exposure in children  $\geq 3$  months to  $< 6$  years of age. Study had 125 patients.

**Comment: results not yet out but BMS say they are committed to continue development of paediatric formulations.**

## Renal stones with atazanavir

Studies found that kidney stones were four times more common in people taking atazanavir than in people taking other drugs. However they were still relatively uncommon. 1260 people investigated in UK and about one case in 50 patients who were being investigated for possible kidney stones turned out to renal stones that contained atazanavir.

## Efavirenz (EFV)

**Q: EFV on PK - is there any data on how genetics affect the way the body handles efavirenz?**

A: A study designed to determine whether higher levels of efavirenz in the blood are related to side effects of the central nervous system (CNS). CNS side effects, including vivid nightmares, difficulty sleeping and mood changes have been reported in a number of EFV studies. Results found a significant association between genetic factors, race – black and Hispanic - and how quickly EFV is cleared from the bloodstream. Blacks and Hispanics taking EFV should be aware of a potential increased risk of side effects and continue careful monitoring.

**Q: EFV and pregnancy – data shows no foetal defects, are you changing label?**

A: FDA classification remains, different countries may do it in different ways. Waiting to see what the new BHIVA pregnancy guidelines come up with.

**Q: Is there any long-term damage on use on paediatrics?**

A: I don't know.

**Q: EFV is going off patent in 2 years, are there any plans to reduce price?**

A: I don't know.

Hepatitis C trials: PSI-7977 and BMS-790052

Participants in these trials are for mono-infected patients. The meeting wanted to know if they could include a 'protective bubble' in these trials by having proportion of co-infected patients so the investigators could get all the data at the same time. BMS responded that there would be co-infection trials in future.

#### HIV Pipeline

BMS-98600 an experimental once-daily NRTI currently in Phase II clinical trials.

BMS-663068 – attachment inhibitor would be the first drug to target the initial step in HIV attaching to the CD4 cell receptor. It works by binding to the HIV-1 envelope glycoprotein gp120, thereby interfering with its attachment to the CD4 receptor.

Hep C pipeline:

Phase II - BMS-790052 is an NS5A inhibitor and BMS-650032 is an NS3 protease inhibitor.

**Q: Do you have any plans on a co-formulation with Gilead on boosting atazanavir with Gilead's cobicistat?**

A: BMS not aware of any plans.

**Comment: On 26 October 2011, BMS announced that it has entered an agreement to develop and market an FDC of its protease inhibitor atazanavir (Reyataz) with a pharmacokinetic booster cobicistat, currently in development with Gilead.**

Follow up questions to BMS...

- i. Provide/confirm atazanavir dosing recommendations for 3 months -8 year olds.
- ii. Confirm efficacy and safety of capsule and granule formulation.
- iii. Q: Is there any research into a product of d4T without the side-effects?

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#### London HIV drug prescribing survey – Mark Platt

If commissioners had asked companies to tender for their drugs, offer the best price possible and then published the prices, this would be more transparent and does not favour one company. It would secure patient confidence in the process.

Draft printout of survey was circulated in the meeting followed by discussion on how to get survey to as many people as possible. Meeting agreed to go ahead with survey, which will be launched by NAM.

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#### Next meeting:

Date: 20 January 2012

Topic: HIV and TB