

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

Meeting Report CAB 35 – Primary HIV Infection 9 July 2010

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Presentations are all available to download for the July 2010 meeting at:

<http://www.ukcab.net/jul10/index.html>

Members attending

	Name	Organisation	Destination
1	Andrew Chuba	Personal	Manchester
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	Solomon Bogale	Naz Project London	London
7	Elijah Amooti	The African Eye Trust	London
8	Eneya Chuba	Personal	Manchester
10	Godwyns Onwucheka	Personal	London
11	Maurice Herbert	National AIDS Trust	London
12	Memory Sachikonye	UKCAB	London
13	Michael Marr	Waverely Care	Edinburgh
14	Nakamba Ng'ambi	Zambia Leeds Comm Assoc	Leeds
15	Nyambe Mukelabai	Leeds Skyline Services	Leeds
16	Paul Clift	KCH Patients Forum	London
17	Robert James	Personal	Brighton
18	Roger Pebody	NAM	London
19	Rupert Jones	Leeds Skyline Services	Leeds
20	Silvia Petretti	Positively UK	London
21	Simon Collins	HIV i-Base	London
22	Svilen Konov	HIV i-Base	London
23	Tibirico Fortes	NAT	London
24	Tsepo Young	NHS Dumfries and Galloway	Stranraer
25	Winnie Ssanyu Sseruma	HIV i-Base	London

Speakers

Prof Jonathan Weber	Faculty of Medicine, Imperial College	London
Kholoud Porter	CASCADE – Seroconverters Database	London
Louise	MRC CTU	London

Programme

Chair: Silvia Petretti		Timekeeper: 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 Merck – Simon Collins		
10:30 - 11:15	Session One – Early Diagnosis and Primary Infection - Prof Jonathan Weber, Faculty of Medicine, Imperial College London		
11:15 - 11:30	Break		
11:30 - 12:00	Session Two – CASCADE – Seroconverters Database - Kholoud Porter		
12:00 – 12:30	Vienna preview – a guide on what to look out for; podcasts, updates from organisations, the 1 st time IAC attendee – Paul Clift/Silvia Petretti		
12:30 - 14:00	Lunch		
Chair: Silvia Petretti			
14:00 - 15:30	Community meeting with Merck, Q & A		
15.30 - 15.35	Break		
15:35 – 16:00	BHIVA Feedback, UKCAB AOB		
16.00	Close		

Company pre-meeting: Merck

Simon Collins, HIV i-Base Treatment Advocate

Simon Collins is an HIV-positive treatment advocate who works to encourage people living with HIV to take an active role in their own health.

Simon led the discussion to bring attendees up to speed on the afternoon meeting with Merck. He explained advocates the importance of being able to question pharmas about their drugs and the politics involved, plus the CAB etiquette of NOT applauding after a pharma presentation.

Merck 's first drug was indinavir, approved in 1996. It was the best PI was a life saving drug but had difficult side effects now very rarely used, approximately 10 people use it in the UK. CAB's focus is on raising awareness on drug safety and contributed to the awareness of indinavir's severe side effects.

Raltegravir (RGV, Isentress) was the first integrase inhibitor to be approved. Integrase inhibitors work by blocking integrase, a protein that HIV needs to insert its viral genetic material into the genetic material into the DNA of a cell.

In clinical trials RGV reduced HIV viral load to undetectable levels (below 50 copies/mL) in four weeks (normally its 24 weeks).

Meeting discussed RGV's efficacy and tolerability and agreed it is good on both and could be used for:

- Late pregnancy HIV diagnosis could use this to have an undetectable v/I at delivery
- PEP
- Patients receiving chemotherapy
- Transplant patients – no interaction with immuno-suppressants
- Clean side-effect profile, better than EFV, no lipids increase
- Patients with treatment resistance
- First-line if a lower price.

Q: How is it priced? Consultants cannot prescribe it due to its high price.

A: *If there is high demand, price should come down.*

Comment: London is different from other places; I get RGV in Leeds for my child.

Q: Can RGV be used on naïve patients?

A: *It was approved 2007 in EU treatment experienced patients with three-class resistance and maybe an option for naïve patients, but further studies will be needed to establish this.*

Questions to Merck:

- Why is such a good drug still so highly priced?
- It is currently a twice daily dosing, any chance for once daily? Is there any research on drug levels if this changes?
- What current studies is Merck doing?
- What are your pipeline drugs?
- Have you had any case reports to MHRA on unusual side effects?
- Have Schering Plough done any study in treatment-experienced patients and what update data is available?
- Any studies that involve RGV?

Primary HIV Infection (PHI)

Prof. Jonathan Weber, Faculty of Medicine, Imperial College

Prof Weber is the Jefferiss Professor of Communicable Diseases and GU Medicine, and the Director of Research for the Faculty of Medicine based at the St Mary's Hospital campus, within the Wright-Fleming Institute. He is a clinician by training, and has undertaken extensive clinical and laboratory based research on HIV/AIDS, HTLV-I and other STIs.

Prof Weber spoke on the rationale for therapy at PHI as this can have long-term clinical outcome at a time of acute HIV infection. This represents an opportunity where intervention could have long-term benefits for the immune system. PHI is defined by an HIV positive antibody test within 6 months of an HIV negative antibody test.

PHI refers to the initial phase; from infection to up to six months of acquiring HIV infection. It is characterised by a short period of massive viral replication. The goal of early intervention is to preserve immune function ordinarily lost, enhance rapid viral control and limit the size of the HIV reservoir, with the aim of attaining long-term outcome.

The viral load rapidly reaches very high levels soon after infection and there is a marked decrease in the amount of CD4 T cells that leads to a short period of immunodeficiency during which patients may become ill. This destruction of immune system is believed to be quite substantial and probably irreversible.

Viral reproduction - occurs only inside host cells and is called replication, which occurs in these stages:

- Attachment - viral surface proteins bind to host cells receptors
- Penetration - entrance into host cell
- Uncoating - removal of capsid proteins (the shell of protein that protects the nucleic acid of a virus)
- Biosynthesis - viral DNA, RNA and proteins are synthesized
- Assembly - viral proteins and nucleic acid molecules complex to form nucleocapsids
- Release - mature virions "emerge" from the host cell into the immune system

HIV replication process:

- 2 days – virus goes through mucosa to establish infection
- 3 days – goes to regional lymph nodes
- 10-28 days – virus leaves lymph nodes into bloodstream and disseminating over the body.

ART intervention in PHI has been shown to help preservation of the immune system, but the durability of this immune preservation is uncertain. Researchers are interested in studying the interaction between the virus and CD4 cells and whether short-term treatment can prevent or alter or limit the damage caused during this early phase of disease. The Short Pulse Anti Retroviral Therapy at HIV Seroconversion (**SPARTAC**) study is currently investigating the possible benefits or risks of early HIV therapy.

Q: Was it possible to reduce to peak of viraemia? Could you eliminate CD4 decline?

A: Studies have shown that treatment in PHI demonstrated enhanced clinical outcome for those receiving ART to those not on therapy.

Comment: Most people do not know when they have been exposed to HIV and only present when they are ill.

Short Pulse Anti Retroviral Therapy at HIV Seroconversion (SPARTAC)

SPARTAC is a randomised-controlled trial comparing three different strategies of treatment in patients recently infected with HIV, referred to as Primary HIV Infection (PHI). The main objective is to determine whether being treated at primary HIV infection for limited duration delays damage to the immune system and consequently prolongs time to initiation of long-term anti-HIV therapy.

SPARTAC enrolled 371 individuals randomised into one of three arms:

- Long Course combination Anti-Retroviral Therapy (LCART) for 48 weeks
- Short Course combination Anti-Retroviral Therapy (SCART) for 12 weeks
- No Anti-Retroviral Therapy

Results from SPARTAC Study are due in 2011.

There are no firm guidelines on how to treat PHI, the science behind the study is:

- Early diagnosis should provide a better response to treatment.
- Treatment can be initiated before the immune system is severely damaged and opportunistic infections take hold.
- There will be less opportunity to spread the infection to others before the person's status is known.

Whilst the chance of early diagnosis may seem attractive, the reality is that early diagnosis is not often made and the disease is not usually diagnosed until the patient presents with opportunistic infections.

Reasons for this include:

- The patient may not present to a doctor with the early illness.
- Doctor misses diagnosis

Q: Timing of treatment; when should treatment start? HIV will have already gone into reservoirs.

A: The study will answer that question, there is no answer at the moment.

Q: Are there any particular drugs used for the study?

A: It is up to physicians, although it is recommended to use combivir and kaletra. This is taken by 90% of patients in study.

Q: Is 3 ½ years enough time to have results?

A: CASCADE – requires at least 170 endpoints for a significant result, currently have 186 endpoints

Q: How do you know you have PHI?

A: There is a criterion for PHI (see earlier notes), or present at hospital and have positive test without a record of a negative result, negative HIV test within 6 months and a positive one.

Q: PHI or acute infection?

A: PHI is described earlier in this report. Acute infection occurs 2 - 4 weeks after HIV infection, usually has no symptoms and is often misdiagnosed.

Q: Do you see a lot of HIV-2 patients in the UK due to migration? Progression takes 30 years?

A: Most patients in the UK have HIV-1. The number of people infected with HIV in West Africa and diagnosed in the UK has increased in recent years, and there is evidence of heterosexual transmission within the UK from people infected in West Africa.

Q: Would you start and stop ART?

A: I would prefer patient to be on treatment forever.

Concerted Action on SeroConverters to AIDS and Death in Europe (CASCADE)

Kholoud Porter, MRC Clinical Trials Unit

Kholoud Porter is a Senior Epidemiologist (project leader) at the MRC CTU working on the CASCADE database.

CASCADE was established in 1997 as a collaboration between the investigators of 22 cohorts of people with well-estimated dates of HIV seroconversion (seroconverters). It is currently a network of epidemiologists, statisticians, virologists and clinicians from leading HIV institutions in 13 European countries, Australia and Canada. Seroconverters are enrolled into the individual cohorts locally and nationally, and are typically followed up for life.

CASCADE's main aim is to monitor newly infected individuals and those already enrolled in studies,

covering the entire duration of HIV infection. The main premise is that through pooling data issues will be addressed, which cannot be reliably addressed from single studies alone. The UK register has about 2500 individuals with well-estimated dates of seroconversion from 116 UK clinics.

Kholoud explained the process of early HIV infection and defined:

- Acute infection – when amount of HIV in the blood gets very high within a few days or weeks after HIV infection. This happens in about 4-6 weeks of infection.
- PHI –the period within six months after a person becomes infected with HIV.
- Seroconversion is the incubation time in which a person has been infected with HIV, but does not yet test positive. Seroconversion occurs before enough antibodies are produced to indicate HIV positive test results using standard HIV antibody tests (ELISA). The seroconversion period for HIV can range from 2 weeks to 6 months, in which time the virus can be transmitted with no sign of infection.
- Early infection – happens within 12 months of seroconversion.

Intervention may be hope of long lasting viral control but some observational studies have differed on findings. Some people treated during this period were even able to control HIV later without drugs. However, the effects did not last in these small studies and no overall benefits could be demonstrated for the patients. More research is still needed in this area. The challenge with PHI is its contribution to onward transmission as viral load is extremely high and the infected person may not be aware of that they are infected.

Comment: Maybe some people later benefit from earlier treatment. There is little data; SPARTAC will have more detail when they present data in 2011.

Q: How does someone know they have just been infected?

A: The onus is not on the patient, if they do not know, we do not know. They need to be diagnosed first.

Q: Would you recommend taking ART 12 hours prior to having unprotected sex?

A: NO! I would recommend using a condom, if there's a condom break then get PEP.

CASCADE works with seroconverters:

- To collect follow-up data that relates events to the same time since an individual first became infected with HIV.
- It is a unique opportunity to study HIV throughout its whole infection period.
- Allows researchers to examine characteristics of recently acquired HIV infection in population, and changes to this over time.
- To aim towards early diagnosis: seroconverters represent what may be achieved optimally.
- There are relatively few in any one clinic/study, it is ideal to collaborate with other centres.

Survival rates in the UK following HIV seroconversion have continued to improve over time with a 97% reduction in the risk of death in 2004-2006 compared with pre-1996 era. Recent studies have indicated that, even in the HAART era, mortality rates among those who are HIV-infected are still at least four times that of the general population, indicating room for further improvement.

Patients newly diagnosed with HIV, commonly expect to delay HAART for 5-8 years. However, the UK Register of Seroconverters has previously reported that at least a quarter of patients may need to start treatment within two years of infection.

A priority for CASCADE is to explore ways to ascertain and characterise the foci of recent HIV epidemics in Eastern Europe, and the varying levels of intervention against them. This will help in the understanding of likely future transmission dynamics across the European region. As HIV positive persons are now expected to live longer, it is likely that non AIDS-related causes of death will become increasingly important; particularly as adverse drug reactions might also have an impact. CASCADE is also looking into whether co-infections, such as HBV and HCV, accelerate HIV disease progression and vice versa.

IAS - Vienna 2010

Paul Cliff and Silvia Petretti

Paul and Silvia are UKCAB Steering Group members. They shared a preview and a guide for the first-time attendee on what to look out for at the Vienna Conference. They have attended several international AIDS conferences in the past. Both said it is a huge conference and easy to get overwhelmed.

Paul's overview

The conference could have about 25 000 participants, covering everything HIV related and there will be pre-conferences on other issues. Advised those attending to watch the opening night which leads to the conference the following day. He highlighted the conference tracks, oral sessions, poster area, plenary, exhibition, global village, etc.

- Track A: Basic Science
- Track B: Clinical Sciences
- Track C: Epidemiology and Prevention Sciences
- Track D: Social and Behavioural Sciences
- Track E: Economics, Operations Research, Care and Health Systems
- Track F: Policy, Law, Human Rights and Political Science

For a first-time attendee at the conference, his final emphasis was that attendees should not try to cover everything, select and try to focus on one track. Use of conference website programme to plan a personal roadmap. He encouraged attendance of the rapporteur session at the end of the conference as it gives a useful summary of the main outstanding points. He also urged attendees to be ready to learn and get breaks during the conference, use the PWA Lounge.

Comment: For those not attending the conference, podcasts of the presentation can be watched online.

Silvia's overview

She has been working on the Leadership and Accountability Track for the last 18 months. Her input was to ensure there is a positive person at each plenary session. The conference will be asking government leaders about universal access on prevention treatment and care as set in the MDG. She shared her slides from the previous conference in Mexico.

This year's conference is being held in Vienna to highlight the growing HIV rate in nearby Eastern Europe and Central Asia, which is fuelled by intravenous drug use. Silvia urged CAB members to sign the "Vienna Declaration", which says the criminalization of illicit drug users is fuelling the epidemic and calls for a full policy reorientation.

Comment: Dr. Elly Katabira of Uganda will be the first African president of the International AIDS Society for the next two years.

Company meeting with MERCK, Q&A

Merck's reps did not have any slides and informed the meeting they wanted an informal Q&A. The meeting's questions to Merck were:

Raltegravir pricing, access

Q: What is the price of RGV in the UK; England vs Scotland vs Wales?

A: After price negotiations it changed on 1/1/10 and varies from £21.40/day to £20.54/day. It was approved in Scotland in May 2010.

Q: Is there a discount for different areas? How does that compare to the retail price?

A: It's difficult to be specific about discounts; information is too sensitive to share.

Q: When RGV was approved it was for treatment experienced patients and Merck was able to charge higher, now data shows otherwise and you are dealing with a higher market. What significant difference does RGV show over other drugs?

A: There are so many factors in terms of choice; it depends on decision-makers on where the drug will be used. It is also affected by global pricing of drugs; we offer a lower-tier price system.

Q: What are the clinical features of RGV that are beneficial?

A: From a medical perspective it has a good profile on efficacy, tolerance, CNS and toxicity.

Comment: It is a great drug, but not affordable. As a pharma you could have a lower price for RGV if more people are taking it.

Comment: RGV license changed in September 2009 and intend to enable access to as many people as possible at a price that value of RGV.

Comment: Some people in this meeting cannot access RGV as doctors raise the issue of cost-effective drugs and therefore cannot prescribe it.

Q: What is your pricing standard?

A: Different parts purchase at a different price up to 10%.

C: There is lack of transparency on pricing and need to be discussed with the HIV consortium.

Q: Are you sitting and waiting for something to happen or do you go and say this is what the community wants?

A: We are interested in knowing what the community wants and we will take that back.

Q: Is RGV safe for use in women, or for MTCT?

A: It is safe for women but not licensed in pregnancy, there are no adequate and well-controlled studies in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Q: Have there any case reports on RGV to MHRA since licensing?

A: When updating the label, that will be highlighted when changing the label. There was one severe case of Stephens Johnson Syndrome (SJS).

Q: Any studies to adjust the diarrhoea side effect?

A: There is no dosage adjustment with other drugs. The ingredients contain lactose which can cause diarrhoea that cannot be excluded in the tablet formulation.

Q: What studies are you currently doing?

A: Current studies are SPARTAC, and one in US which will report in 2011; study of RGV 800mg once daily dose that will report at CROI 2011. There is no data on benefit on dosing, if its goes any lower it may not work. There is also no data on brain barrier; other studies show that it penetrates the barrier well.

C: The CAB expected specific answers since drug was approved rapidly on a small number of patients. What about the FDA data on depression?

A: The cases were four patients who were taking anti-psychotic meds and the regulators think there is doubt of serious side effects.

Q: What about paediatric formulations?

A: There is a chewable tablet for paed under 12 years, with data update CROI 2011. We are developing a syrup formula peads under 2 years.

Q: Are you working with labs to track INI resistance test ?

A: Any lab doing resistance tests can do an INI resistance test.

Q: What is the update on the CCR5 inhibitor?

A: As part of its recent merger with Schering-Plough, Merck acquired vicriviroc (CCR5) to be used for treatment-experienced patients. But due to disappointing clinical trial results Merck continues to evaluate vicriviroc as first-line therapy for treatment-naive patients.

Comment: Entry inhibitors work by preventing HIV from infecting human cells. In order to infect a cell, HIV must recognize and bind to a receptor on the cell's surface. Once HIV is attached to the cell surface, it can enter and infect the cell. Vicriviroc is a small molecule that binds to one of the cell's HIV receptors called CCR5. Vicriviroc blocks HIV from attaching to CCR5, preventing the virus from entering and infecting the cell.

Q: Whilst you wait for CCR5 development in the UK, who is your biggest competitor? Maraviroc?

A: U.S. market is bigger and not aware of CCR5 being used in the UK. Maraviroc became accessible in Scotland after the Scottish Medical Council review, not sure on uptake. It is also accessible in Leeds; doctors in Leicester can prescribe any drug.

Q: Global access – will you offer licences for generic drugs?

A: Over 70 countries have regulated access to generic RGV; e.g. India. We are aware of need for global access, need more information on how that will work. There is a global approach to pricing, we are trying to do something about generic licensing and have in Bots and hope to have that replicated.

Q: What you presenting at IAS (Vienna 2010)?

A: There are no Merck studies, but are sponsoring a switch study on switching from a lopinavir to RGV.

Q: Which drugs are best used with RGV?

A: RGV can be used with two nukes as a first line treatment, but is usually saved for second line treatment.

Q: What are Merck's pipeline drugs?

A: Merck is still looking into HIV vaccine after STEP did not work. Also looking into new PIs and NNRTIs. Merck is about to release data on raltegravir on herpes treatment and MK709 for Hep C.

Q: Is there any study for a drug on Hep B for African patients?

A: Merck already has Hep B and Hep C vaccines.

Q: Is that a commitment from Merck that you are active in the HIV drug development?

A: We have a very strong portfolio in drug development.

Q: Are supporting any studies?

A: We are looking at patients switching from Truvada; MRC 2nd line treatment in Uganda, Zimbabwe and Malawi; PK studies, basic science research RGV and the START study.

Comments on meeting with Merck:

A community discussion followed and agreed:

- Merck seemed very unprepared, did not bring any slides. They were mumbling, too much floundering.
- Merck however seems to be interested HIV and are supporting studies in the UK, but missed opportunities to talk about their good work.
- The paed sprinkle formulation is a good idea, suggestion for Polly Clayden from i-Base do a talk to the UKCAB.
- The meeting agreed that the Cab should give better briefing to the pharma, prepare what we should expect from pharmas. We should follow up with an email on outstanding issues not answered today.

BHIVA Spring Conference feedback

There was a strong community involvement, good poster presentation and Silvia Petretti identified one on teenage pregnancies and it won. There was a poster on testing children, need something more scientific research, try and get abstracts in.

AOB

Announcement - publications from HPA for all to take, including STARHS test leaflet.

Next meeting: 22 October 2010
Topic: Getting the most of your GP