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Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

# HTLV-1 Special Interest Group Roundtable 2

## 8/11/17
## National Convention Centre, Canberra

Attendees:

- **Professor Damian Purcell, Professor of Virology, Doherty Institute – Chair (DP)**
- Associate Professor Marisa Gilles, Public Health Physician, WA Midwest (MG)
- Dr Katelin Haynes, Queensland Program Manager, ASHM - Secretary (KH)
- Dr Fabiola Martin, University of Queensland/University of York (FM)
- Dr Genoveffa Franchini, Head of Animal Models and Retroviral Vaccines Section, National Cancer Institute Centre for Cancer Research (GF)
- Shane Schinke, person living with HTLV-1 (SS)
- Professor John Kaldor, Program Head, Public Health Interventions Research Group, Kirby Institute (JK)
- Dr Gill Schierhout, Aboriginal and Torres Strait Islander Health Program, Public Health Interventions Research Group, Kirby Institute(GS)
- Dr Lloyd Einseidel, Executive Director, Central Australia Baker Heart and Diabetes Institute (LE)
- Professor Graham Taylor, National Centre for Human Retrovirology, Imperial College London (GT)
- Dr Manoji Gunathilake, Sexual Health Physician, Sexual Health & BBV Unit, CDC NT (ManG)
- Dr Kath Fethers, Sexual Health Physician, Melbourne Sexual Health (KF)
- Dr John Zaunders, St Vincent's Hospital Sydney (JZ)
- Associate Professor Paul Cameron, Doherty Institute (PC)
- Dr Rae-Lin Huang, Sexual Health Program Coordinator, Nganampa Health Council (RLH)
- Associate Professor Kerry Taylor, Acting Director, Poche Centre for Indigenous Health and Wellbeing, NT (KT)

Online:

- James Cooney, PhD Student, WEHI
- Professor Marc Pellegrini, Joint Division Head: Infection and Immunity, WEHI

Apologies:

- Associate Professor David Anderson, Deputy Director (Partnerships), Burnet Institute
- Dr. David Yurick, Doherty Institute
- Associate Professor Michelle Giles, Alfred Hospital
- Professor Paul Young, University of Queensland
- Dr Vicki Krause, CDC NT
- Clinton Pepperill, Aboriginal Research Officer, Flinders University

Meeting opened by DP, acknowledged the traditional owners of the land on which the meeting was held, the Ngunnawal Nation.

1. **Presentation by Kerry Taylor** – the historical context of HTLV-1 in central Australia and how this impacts on research and public health policy.
    - Aboriginal people are the 'most researched' population in Australia and experience research fatigue.
    - In the past, "informed consent" has not always been informed. People did not understand the research, or how their information/samples would be used.
    - LE has established good links with the community and conducts work which is culturally safe
    - However, unethical and culturally unsafe research has been conducted in Central Australia in living memory, including on HTLV-1
    - For example, publication of the names of communities with high rates of HTLV-1, also operating without local ethics approval
    - Cultural safety means working with, not on, Aboriginal people. Draws on concepts which already exist in Aboriginal culture to foster understanding and collaboration.
        - Cultural safety is not just about race – it encompasses any systemic or unconscious bias
    - The community must be engaged before any research begins, and all aspects of the community engaged, not just the target group. Important to work with the community holistically and inclusively (don't assume what people want to know or participate in).
    - Feedback to the community is very important, but must be done in accessible, acceptable ways

LE – Indigenous health research worker, Ricky Mentha brought a message from the Aboriginal Health Congress to the Global Virus Network meeting in Melbourne in September 2017 that they are happy to collaborate in a research program on HTLV-1. Current work reports back to both Men's and Women's subcommittees at the Central Australia Academic Health Science Centre (a Centre of Innovation in Regional Health).

**Action Item: Annual meeting with representatives from relevant communities should be conducted to feedback the progress of HTLV-1 research, including basic science and any research conducted on samples collected from the population.**

Clare Hubbarts (sp?), Public Health Physician working in the Goldfields region should be invited to future meetings.

2. **Presentation by Lloyd Einsiedel** – Responding to clinical demand: HTLV-1 research in Central Australia

- Gaps:
    - Epidemiological data is currently only comprehensive in a small group of local communities. Picture across the country still unclear.
    - MTCT burden still unclear – current recruitment only of school aged children.
- Current community cohort recruited 750, expected to hit 1000 by mid-2018. 23% of the cohort have HTLV-1 related disease – largely lung disease and neurological injury.
- Bronchiolitis (precursor to bronchiectasis) should be a priority for treatment.
- Contribution of blood stream infections in HTLV-1+ is under-recognised. Blood stream infection rate is 3% annually in town camps, which is 40x the level seen in non-Indigenous populations. Antoine Gessain's work showed that HTLV-1 proviral load is related to blood stream infections.
- Priorities for work:
    - Define the epidemiology in a wider fashion across the country
    - Mechanism to identify people with early disease – spirometry, time to walk
    - Treatment research
    - Public Health response
    - Vaccine
- Community was quite upset that half the community was affected and nobody knew anything about it

Discussion

JK – Informed consent for an individual is different to informed consent for a community, and it is unclear how to ensure this process is understood and done appropriately. Question isn't are we ready for the next research or public health step, it's are the community ready?

FM – Are the community ready for the next step and what can we offer? What monitoring tools are available? These should be developed and implemented in consultation with affected communities.

LE – Spirometry is an early monitoring system which seems to be efficacious, predictive and acceptable. But this is a clinical solution – the priorities must be set by the Aboriginal communities.

DP – We have developed a droplet digital PCR assay that accurately measures the percentage of infected T-cells in blood, the proviral load per T-cell, and also in sputum and other inflammatory exudates. Increases in the percentage of HTLV-1 to 1% or greater of T-cells using this ddPCR assay correlates with onset and progression of disease.

GF – Another option is to further profile the chronic inflammation, as many of the elevated cytokines are druggable, either available or in development. Unclear how acceptable would this be to the community.

JK – Great care is required when going in to these communities. Such a high positivity rate can tear a community apart. This is the most complicated public health issue that I've ever come across.

GT – This is an ancient virus which migrated with these people thousands of years ago. Has that been used as an angle to "normalise" or explain the infection to communities?

KT – We haven't focused on that aspect specifically with communities. We focus more on how people used to look after their country and themselves, and encourage them to do this again.

GT – A lot of our asymptomatic carriers in the UK clinic have a reduction in airway flow, however the mortality rate is not the same as in Central Australia.

JK – This may be related to the high background rates of infection in Central Australia compared to UK.

KF – any interaction with rheumatic heart disease? LE – No.

3. **Presentation by Marc Pellegrini and James Cooney** – Update on animal models of HTLV-1 infection
    - Mouse model of HTLV-1 infection suitable as a preclinical research model for HTLV-1c and HTLV-1a.
    - Immunocompromised mice which are injected with human stem cells after 24hrs, which reconstitute the bone marrow with human cells susceptible to HTLV-1 infection.
    - Proviral load reaches steady state within three weeks following infection. Every T-lymphocyte appears to be infected in these mice, perhaps because they don't have a fully competent immune system. Steady state is maintained as long as they have been monitored out.
    - Lymphocytosis occurs in the mice with log increases in CD4 and CD8 cell numbers accompanied by hepatosplenomegaly and flower cells.
    - The model is ideal for use in investigating the efficacy of therapeutics such as current antiretrovirals in use for HIV as reverse transcriptase is active in HTLV infection.
    - MP and JC have tested a current antiretroviral medication as pre-exposure prophylaxis for HTLV-1 in their preclinical research model and initial experiments **have been effective at abrogating HTLV-1 infection in-vivo**.
    - The treatment was effective even with a high infective load, and in cells which are not fully immunocompetent – a model stacked against finding efficacy.
    - Further experiments titrating the dosage are needed to determine the therapeutic dose, which may be much higher than that needed to treat HIV.
    - The medication is already licensed for the treatment of HIV and HBV in Australia, which removes many barriers to clinical trial.

- In the high dose challenge model when the medication was administered at an early time point post-exposure, proviral load started to increase again 4 weeks post infection – may be indicates sites where he drug isn't reaching – but more experiments are needed to understand what is occurring.
- Another option is to target cell death pathways. Potential agents for these studies are also under investigation.
- Immediate experiments:
    - Conduct head to head comparison
    - Titrate dosage
    - Scale back number of cells used for initial infection to more closely resemble natural infection situation

Discussion

DP – This is a viable therapy for PrEP for HTLV-1.

FM – INSTI or Zidovudine could be trialled in combination with the medication. Also the option of PEP or PrEP.

JC – Raltegravir had no effects on transplant patients with HTLV-1.

FM – But that was post-infection therapy. Should try comparisons with dual or triple therapy.

MP – Yes we should try that, if we had enough (any) funding. Might try the medication on its own first.

PC – How much of a telomerase effect will this dose have? Is this a true antiviral effect or an effect on cell proliferation?

GT – Clonality is the real question which needs to be tested. Is this a lack of proliferation or something else? Is it possible to piggyback on current PrEP trials? Need to open a dialogue with companies about how to do this, as it is very unlikely they are currently testing for HTLV-1.

DP – Gilead haven't thought about doing this, at least as at 12 months ago.

JK – Central Australia is a very difficult place to try to test a therapy. Clinicians and clinical trial scientists should get together to come up with a viable framework to test this as a therapy – not necessarily in Central Australia. A Clinical Advisory Group should be formed to provide feedback to JC and MP.

4. **Presentation from Fabiola Martin** – Maintaining the patient-centred approach
    - Feedback from the patient workshop held at the 16th International Conference on Human Retrovirology, Montreal June 2013. Patients want:

    - Eradication of HTLV
    - Therapies which reduce proviral load
    - International standards of care for clinicians
    - Education and motivation of clinicians
    - Happy to participate in placebo RCT
    - Want to be involved in study design
- There are 17 prevention strategies available to us which have already been developed and implemented for other blood borne viruses. For HTLV, the strategies are all available and applicable but have not been implemented (for various reasons), both internationally and within Australia.
- With a majority of transmission (74%) occurring through sexual contact, need to make sure any interventions are focused on this route.

Discussion

GT – International Retrovirology association currently drawing up guidelines on ATLL management and myelopathy management.

JK – WHO not on board with HTLV-1 at this stage, but there is a real need for international guidelines. Guidelines can be written now – they just need the best available evidence, not perfect evidence as they undergo constant refinement. Currently no guidelines at all – Lloyd could contribute hugely to this. Proviral load is a strong predictor of adverse outcomes and the evidence behind this should be put together in a more coherent way ie. review. Should this change clinical management? Need access to proviral load testing to do this, which we can advocate for now.

PC – What about a point of care test? Dried blood spot?

LE – Dried blood spot testing is currently done at the National Reference Laboratory by Kim Wilson, however it isn't very sensitive at low proviral loads (<0.1%).

PC – That's fine, as proviral load > 1% is the predictor for severe disease, so low sensitivity isn't needed. LE & GT agree.

GT – Quantification can also be done from fixed samples – may be a solution to storage issues with samples coming from remote areas.

FM – What about vaccine development?

GF – We know why companies wouldn't buy it in the past, and it's doubtful they would buy in now as it is still too difficult to test efficacy in a population. More basic research is needed to show that it works effectively. Previously worked with Sanofi to develop it. Doesn't include *tax* – based on ALVAC, orf 1 and orf 2. Currently in my freezer in the lab.

MG – If I was an Aboriginal person, I'd want to know – what should I do next? If 22% of transmissions are through breastfeeding, we should be giving advice to mothers about this.

JK – Guidelines on clinical management and wider access to proviral load testing is needed first. Avoidance of breastfeeding is sensitive in central Australia. The Central Australian Aboriginal Congress and LE have started a pilot of screening pregnant women in the past few weeks, starting with asking if they want the test.

LE – Most community members who have been recruited so far don't want to know their individual result, they are participating in screening for their community.

MG – What are the ethics around not returning test results if a positive mother then goes on to breastfeed her child?

JK – sexual transmission can be prevented through abstinence or condom use.

KF – is proviral load related to sexual transmission – yes.

JK – Sexual transmission of HTLV-1 can only be prevented by abstinence or condom use. The only demonstrably effective STI response in central Australia relies on a test and treat strategy, which won't work for HTLV-1 because no treatment is available. Blood to blood transmission can be prevent by NSPs and universal precautions in a healthcare setting.

FM – On WHO website, HTLV-1 document is 15 years old and gives poor and inaccurate advice.

5. **Presentation from Shane Shincke** – The patient perspective.
    - Lack of information about HTLV-1 is very upsetting, from both medical professionals and on the internet.
    - Care must be taken not to separate the response to HTLV-1 into Indigenous and non-Indigenous – all patients should be treated under the same guidelines
    - Any response – public health or clinical - should start with the community and expand from there.
    - Awareness and education of health professionals must be improved for the patient diagnostic journey to improve.
    - Epidemiology needs to be a focus, as we don't know what is going on in the non-Indigenous population because we haven't been testing.
    - Have to be very careful when taking this public, talking about sex is still very taboo in Aboriginal communities. Classifying it as a sexually transmitted disease puts it in a box which may be limiting.

Discussion

JK - Alliance of Australian Academic Health Research Translation Centres has an Aboriginal Health subcommittee (JK is a member), which had its first meeting a few days ago. This may be an ideal group to bring in to consult on guidance for clinicians and patients. Another way to get it on to the National agenda. Centre for Innovation in Regional Health would still take the lead on any research or grants.

SS – Raising the profile of HTLV-1 too early runs the risk of losing people or momentum, if awareness is raised but no solutions are provided. This is a very sensitive issue with very complex cultural aspects. There is a real risk of headlines of "another Aboriginal sexual disease". Community engagement isn't a cliché, it is the most important factor in a successful response. Keep in mind that there is no single "Aboriginal people" – each community is different and unique.

**CRE Application Discussion**

JK - CRE's are assessed under five criteria. Number one carries all the weight in deciding which grants are successful.

1. Contributing new knowledge which will resolve a significant health issue
2. Translating your knowledge into policy
3. Capacity building of both the clinical workforce and the community
4. Collaboration and communication
5. Track record of applicants

The other important thing which isn't scored, but carries a lot of weight are the Indigenous Research Criteria:

1. Health benefit to Indigenous populations
2. Community consultation
3. Capacity building
4. Sustainability and transferability

It is possible to include international investigators on CRE applications. Grants are primarily scored on Chief Investigators. Don't have more than 10-15% overseas Chief Investigators, can have more in Associate Investigators. CRE due in three weeks **today**. 20 pages. Realistic to write this year? Should we wait until next year?

LE - CRE application – 2.5 million over 5 years. A lot of unanswered questions in HTLV-1. What do we invest in what? I propose:

- defining the endemic area and number of people infected
- identifying people with early disease
- developing structure around referral pathways and education of clinicians
- improve understanding of pathogenesis
- new assay development
- further investigate inflammatory cytokine profile
- further funding to support prospective cohort recruitment

- Need to understand more about the pathogenesis. New assay development. Understanding cytokine profile.

MG - Occupational PEP guidelines for HTLV-1 in NT recommend Truvada – does any other jurisdiction have this?

FM – No evidence for Truvada as PEP – Raltegravir should also be co-administered with Truvada as a retroviral INSTI.

DP – there any many other funding opportunities.

Headings for the CRE application will be circulated around the Special Interest Group. Participants are welcome to contribute to the application.

**Priorities for work:**

- Define the epidemiology in a wider fashion across the country
- Mechanism to identify people with early disease and ongoing monitoring – spirometry, time to walk, proviral load
- Treatment research – for treatment and PrEP
- Public Health response – breastfeeding advice at least. Partner notification?
- Vaccine – GF has a vaccine in the freezer, no interest from companies to develop further. Happy to collaborate to continue development.
- Guidelines for clinical management
    - Update of WHO information
    - Develop Australian(/International?) management guidelines
- Advocate for wider access to proviral load testing
- Community engagement
    - Yearly feedback meeting including basic science
    - Approach Alliance of Australian Academic Health Research Translation Centres - Aboriginal Health subcommittee
- Write review of proviral load as clinical monitoring tool
- Many of the above can be addressed in the CRE grant application