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Developing a sustainable HIV, viral hepatitis and sexual health workforce

HTLV-1 Special Interest Group Meeting Minutes

Wednesday 18th September 2019, 2:00 – 5:00pm (AWST)

Meeting Room 9 – Perth Convention and Exhibition Centre, 21 Mounts Bay Road, Perth

Chair – Professor Damian Purcell, Department of Microbiology and Immunology, Peter Doherty Institute

Attendees:

In person	Teleconference	Apologies
Charlie Gilks Damian Purcell Lucas de Toca Rebecca Newton	Katelin Haynes Manoji Gunathilake Fabiola Martin Paul Young Marc Pellegrini Pip Hetzel Andrea Fisher	Scott McGill James Cooney Kath Fethers

Agenda

1. Acknowledgement of traditional owners
   We acknowledge the Whadjuk Nyoongar people as the Traditional Owners of the land we are meeting on today, and acknowledge their elders past, present and emerging.

2. Introductions
   Charlie Gilks – Head of School of Public Health, University of Queensland
   Damian Purcell – Head of Molecular Virology Laboratory, Doherty Institute and Chair
   Lucas de Toca – Assistant Secretary, Indigenous Health Division, Australian Government Department of Health
   Rebecca Newton – Director, Blood Borne Viruses, Sexually Transmissible Infections and Torres Strait Health, Office of Health Protection, Australian Government Department of Health
   Katelin Haynes – Quality & Improvement Manager, ASHM
   Manoji Gunathilake – Sexual Health Physician, SHBBV Unit, Centre for Disease Control, Northern Territory Department of Health
   Fabiola Martin – Sexual Health Physician, Queensland
   Paul Young – Head of School of Chemistry and Molecular Biosciences, University of Queensland
   Marc Pellegrini – Joint Division Head, Division of Infectious Diseases and Immune Defence, Walter and Eliza Hall Institute
   Pip Hetzel – Director, National Reference Laboratory

Andrea Fisher – Executive Officer, Viral Infectious Diseases, Doherty Institute

3. Update on outcomes from National Collaborative Forum on HTLV-1 - **Lucas de Toca & Rebecca Newton**
   Baker Institute have made an application to the Commonwealth for a longitudinal study to examine the prevalence and disease associations with HTLV-1. No contract has yet been mutually executed, but something is expected relatively soon. This is a direct outcome of the National Collaborative Forum in Alice Springs in August 2018, and will have a strong Aboriginal Governance structure and community engagement.

   Further opportunities for funding may become more clear following the WHO technical group meeting in Tokyo 13-15 November 2019. The Forum identified that clear action needed to be taken on HTLV-1, but must be carefully considered, and supported by the community. Other elements of the statement will not be addressed by the longitudinal study (i.e. guidelines, therapies and biomedical preventatives), but may be addressed through other (potentially international) mechanisms.

   The Forum has spurred a lot of new research and re-examination of data and was very galvanising for researchers. However, additional funding from other sources (i.e. NHMRC, MRFF) is needed to progress much of this work.

4. Conference feedback from HTLV19 in Peru - **Fabiola Martin**
   Three days of oral, poster and keynote presentations in Peru, April 2019. Some highlights from the conference:
   - **Flow cytometry to detect ex vivo early, de novo HTLV-1 infection** - Peres C, Martin F and Fox J. New method to detect new infection, rather than having to perform a DNA extraction (and destroy the cells). Successful at detecting transmission and block of transmission. See published paper.
   - **Quantification of HTLV-1 provirus in plasma cell free DNA** – Joris et al. New method for the measurement of cell-free HTLV-1 proviral DNA. Very important in Australia, as cell-based methods are difficult and expensive to employ in remote communities.
   - **New IRVA Guidelines for the management of HAM-TSP** – See the Guidelines. For patients with HAM/TSP – aim to enrol in clinical trial, or if not available use corticosteroids as first-line therapy. Treatment with interferon or HIV antiretrovirals is not recommended.
   - **Revised Adult T-Cell Leukemia-Lymphoma International Consensus Meeting Report** – See the paper. Revised guidelines on the classification and treatment of ATL patients.
   - **Progress report on long term anti-CCR4 antibody (mogalizumab) in patients with HAM/TSP** – Sato et al. Followed 18 patients with

HAM/TSP while they received low dose Mogalizumab for 18 months. Resulted in reduction in inflammatory markers in the CSF, proviral load in peripheral blood and significant clinical improvement. Side effect included rash, leukopenia and lymphopenia (grade 1-2).

- **HTLV-1 in South East and North Queensland, Australia** - Martin F et al. Screened 2000 samples, 6 reactive, 2 Western-blot positive. 1 Indigenous, 1 non-Indigenous. Coupled with a new publication from Smith et al, which found 4 HTLV-1 positive patients (3 in the same family) from 444 tests in Far North Queensland between January 1999 and December 2016. Positive patients had ATL and scabies.
- **Characteristics of non-TB pulmonary diseases among HTLV-1 positive people** – Cachay et al. 53 patients with HTLV-1 infection had non-TB lung disease; 64% women; 51% other HAID: 15 HAM/TSP, 8 IDH, 3 ATL, 3 uveitis. Proviral load of patients was not provided, but other research suggests it is high in symptomatic individuals.
- **Risk of HAM/TSP after HTLV-1 via kidney transplantation** – Jamuchi, J. 10 Donor positive, recipient negative: 4 cases of HAM/TSP within 3.5 years post transplant. 30 Donor positive, recipient positive: no cases of HAM/TSP or ATL. 59 Donor negative, recipient positive: 1 case of HAM/TSP plus ATL. Transplantation of positive organs is not banned in Japan.
- **Self-flagellation as a route of HTLV-1 transmission** – Tang et al. Muslim cultural practice. 10 cases, 2 mothers tested negative (8 untested)
- **ATL in Brazil** – Rosadas et al. From epidemiological data, would expect more ATL than is reported. Estimated 256-800 cases/year, but only 12 cases/year are reported in Brazil. Reasons: ATL is underdiagnosed or misdiagnosed due to a lack of training of health care professionals. People can also die very quickly from ATL, in this setting perhaps without accessing healthcare.
- **High mortality in HAM/TSP** - De Moura et al.
- **Bone fractures in patients with HAM/TSP** – Tipismana et al. Bone fracture is a risk factor for disability and mortality in HTLV-1 patients.
- Depression and Quality of Life in patients with HAM/TSP – Ramos et el. 95 patients with HAM/TSP, mean duration of 10.5 years. 54% reported depression, 31% suicidal ideations and 43% low QoL.
- Public policies for people living with HTLV – analysis of the government agenda (Bahia and Rio) – Garcia et al. Influencers who led to the finalizations of policies, which rolled out public health HTLV prevention strategies and HTLV service provision included researchers and health professionals. But importantly

also 'social actors': NGO, social workers, health advisors, community members, patient advocates.

A full report from the meeting is expected to be published soon.
James Cooney presented on a replication competent humanised immune system mouse model, which has been used to test an ARV approach to preventing transmission.

5. a) HTLV-1 and MRFF/other research funding opportunities - **Damian Purcell**
Opportunity for us to better understand HTLV-1c strain, and research prevention mechanisms.

Virology - from sequencing, Purcell group is showing variation between HTLV-1 strains is not as great as HIV, so vaccination may not be as difficult as for HIV. But a clinical trial of a vaccine in the field (in Australia) may be very difficult. Vaccines under trial internationally are currently targeting prevention, rather than therapy. Genoveffa Franchini (NIH) has a therapeutic vaccine in the freezer at NIH, waiting for someone to test it further.
Three papers have been submitted by Damian and co-authors on variation in regulatory gene structures of: (1) p12/p8, (2) p30 and (3) on HTLV-1 proviral genome deletions in patients. The latter study showed virus structural gene occur at high frequency in HTLV-1 infected individuals. Deletions are most common in the *gag* gene, but provirus retains X-region (promoting proliferation and survival of cells). As a consequence, antibodies to structural proteins (mostly used in testing) may not be a robust marker for infection. Similarly, proviral load (PVL) assays which target these gag or other structural gene regions may also result in issues resulting in reduced detection. PVL assays should target regions in the X-region that are positively selected for the proliferation of infected cells.

Pathogenesis – Dr Einsiedel is increasingly demonstrating a strong association with bronchiectasis. Further studies examining cytokine profile are planned to explain proliferation of T-cells in the lungs.

Prevention – Marc Pellegrini and team at WEHI have human immune system mouse model, an excellent platform for testing ARV compounds on HTLV-1. Testing Tenofovir alafenamide (TAF) demonstrated an effectiveness at preventing transmission. Possibility for use as PrEP, perhaps in combination with other drugs (of unknown identity). Can also use this mouse model to test therapeutic drugs to reduce proviral load. HTLV-1c and a behave very differently in the model. Subtype C expands very quickly and kills the mice quickly compared to A. Now attempting TAF treatment with potential curative therapeutics (SMAC-mimetics), but very difficult as HTLV-1c spreads so quickly cell to cell. May be easier to investigate this with 1a, since it is more benign. Very long co-evolution

with HTLV-1c and Aboriginal and Torres Strait Islander people, may have resulted in genetic means to limit the severity of infections. Presume all the blood Pellegrini group is using is Caucasian. This is expensive research, but would make an excellent basis for an MRFF application. Marc thinks research would have to be positioned to have very near-term impacts to gain traction at MRFF level.

Preventative vaccines: Paul Young group has been producing trimeric HTLV-1 env, which is a breakthrough reagent as a vaccine candidate. Has been trialled in mice, to promising effect so far (more effective than similar work on HIV). Purcell group has also produced trimeric env through a different mechanism – SOSIP trimer which was recently improved for efficiency of production. Also developing assay to measure antibody-mediated virus neutralisation. Found patients with very effective broadly neutralising antibodies (bNABs). Plans to test the ability to block HTLV transmission after infusion in the HIS mouse model, but need a bigger serum sample from the patient. Aim is to produce a monoclonal antibody to HTLV-1c, but this requires research funding to go forward.

b) HTLV-1 discussion on future research funding opportunities [30 minutes]
Marc has successfully received an MRFF grant in the past. Frontiers grant does not require preliminary data, but his successful grant did have minimal preliminary data. Need to demonstrate near-term impact of the research (within 5 years).
Paul Young – can take a candidate vaccine through a production process to trial at this point. Could move forward with this work relatively quickly, especially with trials in Marc's mouse model. Paul's group is taking a similarly designed subunit vaccine to Phase I in mid-2020, which could lead to faster approval by TGA.
Damian – longitudinal study will create an effective dialogue with Central Australian communities, and now we are approaching a space where we can offer prevention solutions, rather than coming with empty hands. Therapies available internationally are not curative, very focused on end of life. Focus of Australian research is on providing biomedical tools to prevent transmission, analogous to the successful approaches which are already effective for HIV, HBV and HCV (antivirals, PrEP, vaccination). All of this work is currently being undertaken without any funding.
Most work is currently funded through ACH^2. A number of IDEAS grants have been submitted, but success rate for that scheme is expected to be very low (<5%). The dedicated funding afforded to National Centres tackling HIV (ACH^2, Kirby et al) may be an effective strategy for accelerating research in this area, just as it was in developing capacity in the early years of HIV research.
Diagnostics – Purcell recently published a paper on digital droplet PCR. Under development is an automated and high throughput integration

assay (modified from HIV) and could add a measure of infected clonality to proviral load data. Also newly developed is an ELISA assay measuring HTLV-1c gp62 trimer envelope-binding antibodies. Interesting is that sera from patients with the highest levels of NABs also have highest levels of trimer binding antibody. Furthermore, the HTLV-1c Env-trimer binding ELISA data also significantly associates with proviral load. Therefore this Env-trimer binding assay may serve as a proxy measure for PVL suitable for testing existing stored serum. Proviral load is the best prognostic marker for onset of disease – but currently difficult to use on stored samples because it must be done using cells, rather than serum or plasma that has been stored. Damian and Pip will discuss this in person in a few weeks. The use of a cell-associated DNA test is also problematic in clinical trials as it requires a lot more blood collection. Collecting cells massively increases the expense of research in remote locations, so investing in the development of an assay for cell-free detection would benefit the community and research costs, especially in Australia. Home-based rapid diagnostics were a key development to massively expand our understanding of HIV infections and transmission. David Anderson has developed these types of diagnostics before for HIV. POCT before transplantation could also prevent HTLV-1 infection, as testing is slow and previous cases of transmission and subsequent ATL / HAM/TSP have been reported internationally. Finally, a simple assay that distinguished HTLV-1c from HTLV-1a infections would be a desirable addition to the diagnostics needed to monitor infections in Australia.

6. b) Discussion - Should HTLV-1 be classed as a Nationally Notifiable Condition?
   Most other WHO member countries have HTLV-1 as a notifiable condition. However, the experience of other countries is not considered in application to CDNA. A submission to CDNA can be done by many/any groups. Further surveillance is underway in some (State and Territory) jurisdictions which could inform this process.
   Without notification, it is difficult to know prevalence and map HTLV-1.
   All states would need to agree to make HTLV-1 notifiable.
   If it was made notifiable, would it separate HTLV-1a and c? Depends on how the notification was set up and the diagnostic test used.
   Other options to collect information – systematic approach to collecting data at a state level (which is not notifiable), which is then shared between jurisdictions. i.e. enhanced syphilis response (components of which are not notifiable).
   Fabiola Martin added that because HTLV-1 is not notifiable, it is invisible.
   It was commented that HTLV-1 was not included in the keynote presentation at the Australasian Sexual Health Conference on Aboriginal and Torres Strait Islander sexual health.
   Engagement with the Central Australian community on HTLV-1 has not been strong since this time last year. There are serious concerns about breastfeeding. It is easy to say that HTLV-1 doesn't cause any serious

health problems, but we know that isn't true. Coming forward with potential solutions, rather than saying there is nothing to be done may lead to more traction with the community. Both this group and the HTLV-1 working group need to work for better engagement of Aboriginal and Torres Strait Islander communities. Important to continue to seek out health-literate community members. On this front James Ward was invited to join program committee for the international HTLV-1 conference, but no confirmation received yet. Actions on HTLV-1 in Australia, particularly any public health interventions have to be driven by the community, cannot be 'us doing something to them'.

7. Australian priorities for WHO consultation in HTLV-1 [30mins]
   Damian has been invited, and thinks Lloyd has also been invited. Total number of people will be approximately 70, mostly funded by Australia and Japan. 15 other countries are interested to participate. Important moment for HTLV-1 to be recognised by WHO. Fabiola should be recognised and congratulated for pushing this forward with WHO.

8. Summary and next steps [**Chair -** 10mins]
   - A plan consolidating the broad discovery, diagnostic and clinical translation research should be assembled into a draft for an MRFF grant application to attract the much needed research funding to advance the ideas and priorities identified in this meeting. It was recommended that Damian Purcell commence this process that would involve all the groups participating in the research program.

   - The group should look towards identifying Aboriginal leaders who can speak about HTLV infections and help break the stigma within the community.

   - Research programs will all benefit from the establishment of the Aboriginal steering committee as a part of the taskforce grant that will form part of a culturally sound governance framework for research into HTLV in remote indigenous communities.

9. Close at 4:00pm AWST