ashm
Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

HTLV-1 Special Interest Group Roundtable 3

25/09/18
Sydney Masonic Centre, Sydney

Attendees:

- **Dr Lloyd Einsiedel – ID Physician, Executive Director Central Australia, Baker Institute (Chair)**
- Dr Caroline Bartolo – Advanced Trainee ID/GM, Eastern Health
- Professor Charles Gilks – Head of School of Public Health, University of Queensland
- Professor Damian Purcell – Doherty Institute
- Dr Gill Schierhout – Senior Research Fellow, Aboriginal and Torres Strait Islander Health Program, Public Health Interventions Research Group, Kirby Institute
- Dr Guy Krippner – Executive General Manager, Commercialisation and Research Contracts, Baker Institute
- James Cooney – PhD Student, Walter and Eliza Hall Institute
- Joel Liddle – Research Assistant, Baker Institute
- Dr John Zaunders – Senior Scientist, St Vincent's Hospital Sydney
- Dr Katelin Haynes – National Programs Manager, ASHM
- Dr Kath Fethers – Sexual Health Physician, Melbourne Sexual Health
- Lisa Bastian – Program Manager, Sexual Health and Blood-Borne Virus Program, WA Department of Health
- Dr Lucas de Toca – Principal Advisor, Office of Health Protection, Australian Government Department of Health
- Dr Manoji Gunathilake – Sexual Health Physician, CDC NT
- Dr Marianne Martinello – ID Physician, Kirby Institute
- Dr Philippa Hetzel – Director, National Reference Laboratory
- Dr Radwan Talukdar – Postdoctoral scientist, Baker Institute
- Dr Rebecca Newton – Director, BBVSTI, Australian Government Department of Health
- Scott McGill – Deputy CEO and Director of Programs, ASHM
- Shane Schinke – Research Nurse, Baker Institute
- Dr Skye McGregor – Epidemiologist, Public Health Interventions Group, Surveillance Evaluation and Research Program, Kirby Institute
- Professor Tony Cunningham – Executive Director, Westmead Institute

Online:

- Michelle Panizza – Masters Student, UNSW
- A/Prof David Anderson – Deputy Director, Burnet Institute (left after 2:30pm)
- Professor Paul Young – Head of School of Chemistry and Molecular Biosciences, University of Queensland (left at 4pm)
- Dr Lloyd Nash – Chair, Global Ideas (arrived 2:50pm)
- Dr Fabiola Martin – Sexual Health Physician, Metro North Sexual Health Service and University of Queensland (arrived 3:20pm, left at 4pm)

Lucas de Toca

The presentation provided does not represent the views of the Australian Government Department of Health.

$8 million in funding announced at the end of May 2018 to address emerging communicable diseases affecting the Indigenous population, particularly in remote communities. The Government has not allocated funding priorities for this money. Priorities will be set in consultation with Aboriginal leadership as part of a collaborative process. It is not set aside exclusively for HTLV-1, and other diseases can also use this money. Syphilis has a separate allocation of $8.8 mil.

The Collaborative Forum on HTLV-1 held in Alice Springs, convened by the Chief Medical Officer and CAAHSC, on the 28th – 29th August 2018 was the first step in formulating a response to HTLV-1 which is culturally appropriate and safe. The
Forum was a success from the perspective of the government.
Outcomes of the forum:

- The forum reaffirmed the importance of Aboriginal leadership in this process.
- There needs to be a major prospective long-term study, developed in partnership with the affected communities, to work out exactly what impacts this virus is having on people in Central Australia.
- We will be working to develop better access to effective testing options together with clinical guidelines for HTLV-1 associated conditions. Although the forum did not recommend widespread testing at this stage, more research needs to be done to understand where the virus occurs.
- We will continue to work collaboratively to integrate community priorities, research findings, and clinical and public health guidelines into a coordinated approach to HTLV-1 in Australia. This must be a cross-jurisdictional response.
- HTLV-1 resources need to be developed for health professionals and the community (in primary language).

The Office of Health Protection is responsible for BBV and STI policy (including HTLV-1).

Damian Purcell

HTLV-1 key facts:

- 10-15 million infected worldwide (estimate)
- Lifelong infection
- Virus not found in plasma – intracellular – this is important for testing. Can't use the same set-ups we have for HIV
- Transmitted through cell-cell contact
- Little genetic variation – cell mediated division
- Random integration of virus in host DNA, random TCR
- Prevalence unknown in Australia in urban settings, sexual health clinics, prisons, PWID or international (PNG/Melanesia has the same strain – HTLV-1c).

HTLV-1 pathway forward – lessons from HIV

HIV		HTLV-1	
– Testing	✓	– Testing	↻
– Treatments	✓	– Treatments	✗
– Preventives	✓	– Preventives	✗
– Education	✓	– Education	✗
– Confront stigma	✓	– Confront stigma	✗

National (ACH2 / NCHECR / NCSR) and International coordination (WHO)

Charlie Gilks suggested adding surveillance as a priority as well, as this has been very effective in the HIV response. The HIV program at WHO started as a surveillance program. Surveillance for HTLV-1 should include surveillance of associated diseases. The National Collaborative Forum had concerns about the confidence level of HTLV-1 sequelae, so thought national surveillance (i.e. through serosurvey) was premature.

Should HTLV-1 be nationally notifiable?
This can be proposed by any member of the Communicable Diseases Network of Australia. Currently in discussions between NRL, Kirby and Burnett to expand the ACCESS database to include HTLV-1. HTLV-1 prevalence in prisons is currently unknown. There is also the possibility of incorporating testing in the national prisons entrant survey.

Current testing
Immunoassay x 2
Confirmatory serological test – western blot
Immunoassay and western blot are not independent tests, as they target the same region of the virus. The NRL is looking to revive the previously used (and TGA approved) western blot so the tests are independent. It is unclear how testing serum (current practice) correlates with true positivity, since serum is non-cell based and the virus is rarely found outside of cells.
CMO is keen to fast track qPCR (proviral load – PVL) testing for TGA approval to be used as a monitoring test for HTLV-1. qPCR also has the potential to be used as a confirmatory test for diagnosis, but this is significantly more difficult (and expensive) to do, as diagnostic tests are held to a higher standard than monitoring tests.

Considerations for the longitudinal study for the long term and culturally safe storage of:
- Serum
- DNA
- RNA
- Live cells? On country? ACH^2? What is acceptable to the community? Only source for live cells currently is Einsiedel lab.

Lab facilities must be up to processing and storing these samples. Alice Springs hospital only has very basic facilities currently.

A higher resolution PVL assay that is optimised for both HTLV-1 subtypes C and A has been developed by the Purcell group and published very recently. Genetic analysis of the integrated proviruses shows that the genes for the structural proteins of the virus are frequently deleted, whereas the genes that impact on T-cell proliferation and function are retained. This new assay targets regions of the genome that are retained by integrated HTLV-1 provirus and measures the PVL of these copies together with the numbers of target T-cells in blood or other inflammatory exudates (Yurick et al, J Clin Micro, 2019).

In most patients the HTLV-1 PVL appears to be steady over time. However, in almost half of the patients the HTLV-1 PVL over time *per T cell* increases in some patients, while in small number of patients the PVL per T-cell declines over time. It will be important to understand how these dynamic changes in the PVL through time relate to pathogenesis.

Every patient is different, because their integration events (and potentially transcriptomes) are different. Lots of questions to be answered by the longitudinal study, but need live cells for a lot of this interesting virology work.

Palmer (Westmead) and Purcell labs are looking at using the FLIPS assay to sequence HTLV-1 full length provirus. Deletions in the provirus are already known to support the induction of leukaemia. Unknown if this may also be true for inflammatory diseases.

The Doherty (Purcell and Symons labs) are also looking at high throughput integration site analysis using an assay originally developed for HIV.

Cell phenotyping can utilise 20 colour (or 50?) arrays to examine T-effector memory cell expansion, and subtyping which found lower levels of infection in B-cells and macrophages. This work is happening at the Kedzierska lab at the Doherty and will also commence in a collaboration with the Zaunders lab at St Vincent's.

The Pellegrini lab at the WEHI have developed a human immune system mouse model which can be infected with HTLV-1c. This results in a massive expansion of T-cells, with similar phenotypes to HTLV-1 infections in humans. This is a good model for preclinical testing of therapies or preventive therapies (PrEP). NRTIs may be effective on HTLV-1, but other current HIV ART drugs are enzyme specific and are unlikely to affect HTLV-1 as it has quite different enzymes to HIV. They have tested TAF as PrEP and found effectiveness in a low dose challenge of HTLV-1, but this was lost in a high dose challenge. Further work on this is ongoing. NT guidelines currently recommend TDF for PEP if occupational exposure.

Current molecular tools such as cell lines and plasmids have all previously been developed for HTLV-1a. Damian is working to try and make both an immortalised cell line and a plasmid for HTLV-1c. This has been complicated by recent tightening of DAWR importation restrictions on HTLV-1 material.

Paul Young from the University of Queensland is working on developing a trimer clamp for Env antibody mediated immunity.

A T-cell vaccine for HTLV-1 has previously been developed by Genoveffa Franchini (NIH). This has not progressed to large scale primate efficacy trials due to lack of interest from pharma to fund, but was effective in small scale animal immunogenicity models. Andreas Suhrbier at QIMR is taking another approach to develop a T-cell vaccine, but no details or data has yet been presented.

The Kirby is seeking data from QLD, NT, NSW and WA on HTLV-1 testing. National notifications would help, especially with cross border issues in Central Australia.

Scott McGill
ASHM works in a partnership approach, to facilitate and provide expertise into the development of guidelines, policy and strategies to meet the needs of all 3 key stakeholders – community, government and health professionals.

ASHM's role is to administer, manage and support the committee to produce the Guidelines.
ASHM also manages the publication of the Guidelines and the platform through which it would be published e.g. website/hardcover printed resource etc. ASHM also leads on the promotion and promulgation of the Guidelines.

ASHM provides the secretarial service for the Committee and also usually has an ASHM expert member on the committee itself (i.e. not normally just AHSM project staff who represent the clinical knowledge and needs of the membership).

The Committee itself drafts and reviews and finalises the content – offers the expert input and confirms the final guidelines for publication.

Guideline Committee Membership selection:

- Members to be suggested by the HTLV-1 Special Interest Group and Working Group
- Should include clinical experts, relevant organisation representatives and community representatives wherever possible
- The Special Interest Group/Working Group should consider and define whether members of the committee are invited as individuals (with expertise) or as organisational representatives (or a mix of both)
- People with interest, expertise and availability should be considered
- People with expertise in guideline development as a process should be considered too (even if no HTLV-1 expertise)
- What are the expectations of the Chair? An independent Chair or a Chair with expertise to input into the Guidelines process? Will the Chair be an ASHM Board Member?
- Consider the place of an open expression of interest to find members or an invitation-only approach

- Once potential Members are identified and are invited to participate (or if sourcing them via an EoI, then the following should be included in the invitation)
    - no honorarium provided (except possibly for community representative and RACGP representative if it is a condition of their involvement)
    - Realistic expectations of workload, meeting preparation time and meeting schedule as well as any expected travel
    - Travel costs are often paid for by the secretariat (ASHM)
- There should be an opportunity at the first meeting of the Committee to review the membership and ensure all appropriate people and organisations are represented. Anyone missing should be invited before the second meeting

Functioning of the Committee:

- Committee members enter into an agreement
- Members are to declare any potential conflicts of interest at the initiation and there will be a standing item on the agenda to allow declarations of any changes to conflicts. ASHM will record and maintain the CoI register for this committee. CoIs will be published with the Guidelines to ensure transparency
- Meeting scheduling, agenda, minutes etc will all be managed by the ASHM secretariat
- Committee members will agree on terms of reference, which will be useful and practical and referenced often during the process to keep everyone on track

All the key steps of the development of Guidelines should be defined in a project plan before commencement.
Critical steps:

1. Defining the scope:

- Will it cover diagnosis, treatment and management? What about prevention? Comorbidities? Variances between different affected populations? Just Australian guidelines?
- Is the target audience well defined? Language and level of detail will be significantly different if the target is specialist ID physicians with interest/experience in HTLV-1 vs a GP/non-ID specialist/nurse audience. It is very challenging to provide guidelines suitable for everyone, but it is possible to have other supporting resources to help with translating the Guidelines for different audiences (but have the Guidelines for the primary audience)
- What format will it be published in? The detail and role of supporting resources etc will depend on whether it is an online only resource that can be updated regularly or a hardcopy resource only
- What is the likelihood there is ongoing funding to review and update? If there are concerns about ensuring it is sustainable, then the scope should maybe be determined by how quickly it will go out of date. e.g. the depth of discussion given to emerging evidence may vary depending on how likely this information is to become out of date before the next review

2. Timeline – needs to be realistic and achievable, critical deadlines to be identified. Consider a suitable time for launch and work backwards (e.g. a specific HTLV-1

conference with international audience?), likely to be determined by funding timeline too. ASHM has expertise is planning and managing guideline development, so will guide the Committee on what is reasonable.

3. Literature review:
   - Essential – should be documented into a summary as the foundation for the Guidelines and the reference point for any questions in the future
   - Draw on Committee members to suggest the evidence to be reviewed and synthesised.
4. Committee needs to decide on what evidence level will be accepted as the foundation for the Guidelines? Systematic reviews? RCTs? If relying heavily on expert consensus, then a formal consensus-based methodology should be employed (e.g. Delphi study)
5. Role of working groups should be defined in advance, although may need a flexible approach. Allows for smaller, more easily functioning group of experts to meet/discuss a section of the guidelines separately to the main Committee. Need to establish what reviewing function the main committee will have over the outcomes of the working group. Administrative component of managing multiple committees is extensive and should be considered when deciding on a need for the working group. Individual Terms of Reference or equivalent should be established for working groups to ensure everyone is on the same page and equally committed.
6. Are there specific topics to be addressed in the Guidelines requiring expertise from people outside the Committee? If so, process of inviting them and defining their involvement is necessary.
7. The Committee will need to decide on how to confirm the Guidelines are complete. Even if the Guidelines are published online and therefore could be theoretically updated at any point, it is necessary that the development process comes to a close (for everyone's sake – the funder, the ASHM project staff, the committee's time management etc). The criteria that will determine whether the Guidelines are considered finished and approved by the Committee should be established in advance.
8. Is there a role for supporting resources? Should the guidelines be developed with a toolkit to support them? Practical guides which assist health professionals to implement the guidelines? A cheat sheet? Train the trainer education modules? If so, how will these be resourced and who will be responsible for them?
9. It is expected that Guidelines developed by ASHM will have endorsements by relevant organisations and these will be acknowledged in the final Guidelines. Organisations have varying processes and standards for endorsing clinical guidelines. This should be known in advance and criteria for being endorsed should be built into project plan/budget (e.g. some will charge to review, some need to be involved in the development process, some have a long review period etc). Ideally committee members representing organisations which will be asked to endorse the guidelines should be the main contact for this and facilitate the process through their own organisation (more likely to be successful than if ASHM project staff request endorsement).

10. What is the plan for ongoing review? How will this be resourced? Will it be the role of the Committee who develops the guidelines to be responsible for review?
11. Promotion and promulgation – what will the strategy be? How will this be resourced? Communications expertise? Committee members are expected to facilitate the promotion through their own organisational networks where relevant. Important to celebrate finalising the Guidelines and having a formal launch.
12. Monitoring and evaluation plan – defined at the start and appropriately resourced. Process evaluation is important, particularly in how the Committee is functioning. Any issues should be addressed early. Aim to publish evaluation findings.

Other considerations:

- What happens if consensus isn't reached within the Committee? If the process for reaching consensus on the content is outlined in advance, then this shouldn't be an issue. Other aspects such as the best promotion approach etc will need to be agreed on. Role of the Chair is important is exploring the different views and ensuring all have the opportunity to be heard.
- Circumstances change and ASHM acknowledges that people may not be able to commit the time/resources to being involved as initially expected. It is important that committee members are engaged and actively contributing to the process, otherwise an alternative representative may need to be organised.
- Productive meetings are essential and the project will benefit from face-to-face meetings if resources and time allows. Save costs/time wherever possible by piggybacking meetings on to other planned events attracting the majority of committee members already. This may influence the meeting schedule, if the external events are fixed. Should be considered in the project planning stage.

A significant amount of work goes into producing Guidelines, but there is only an impact if the Guidelines are taken up. A communication strategy is integral and it has to be appropriately resourced (it often isn't and/or staff/committee members move quickly on to the next project and this isn't implemented as well as it can be). This should include presenting at high-profile conferences.

Ideally the endorsing organisations will be keen to promote the guidelines, as it demonstrates their engagement in and support of the sector. Regardless, this should be encouraged and supported in an ongoing way, not just one single email alert. Longevity and validity will be guaranteed if the guidelines are published in a medical journal, but this needs planning and resourcing.

Work with the training organisation of the profession to which the Guidelines are targeted and encourage them to be embedded into the training curriculum. Supporting resources may need to be developed to facilitate this. Needs to be awareness that many specialty areas approach training/education institutions to try to encourage them to prioritise their particular topic of interest.

Discussion

Stocktake of other guidelines should also be performed (i.e. bronchiectasis), encourage them to be updated to include HTLV-1 at the same time.

Baker IDI suggested proposal for longitudinal study should also include guidelines proposal, so government doesn't just get an ad hoc list of suggestions.

CARPA will also be redeveloping their guidelines.

Joel Liddle
Remote engagement

Remote community members have some understandable apathy and mistrust towards agencies which engage with them, as it seems there is a new person every day/week.

100-300 people per community on average in Central Australian communities (biggest 800-1000). Federal, state/territory, NGO and other events (philanthropic/sporting). Young people are the hardest to engage (same as anywhere in Australia).

These communities are oversaturated with "agency" engagement, including DOCS and police. This leads to reluctance to engage, due to the high number of agencies and so much change in people and programs. This high turnover results in a lack of continuity in relationships and contributes to the perception that many of these programs have no obvious results for communities.

Interactions are nearly always in English, which people may have a limited handle on. On average, people have low literacy and usually leave school in late primary school.

Some engagements take higher priority than others – health is lower than land titles for example (which may lead to royalties).

Communities are highly mobile, through movement to town camps and public housing in Alice Springs. Funerals are also very regular (sometimes 2-3 a week), which can lead to trips to community being called off at short notice. Men's cultural ceremony can start in September and go to March, limiting you to six months of work – squeezing time even more. Staff can also be burnt out quickly from this short timeframe, poor roads and poor accommodation.

Current engagement model is not that effective – door to door salesmen method in English (HTLV-1 engagement has not used that approach). Language and translation hasn't been utilised to full potential for engagement. There is also further opportunity for health promotion through tv and radio.

People need accessible information about HTLV-1 (preferably in their own language) – the more we talk about this and promote this, people will be requesting testing and information

from their clinics, and wanting their individual results back. Programs must offer choice and autonomy to engage with testing.

Lloyd's study doesn't currently give individual results back, just community level results. Individuals are told to go to the clinic for further testing, but these services are sometimes provided by organisations which are not aware or motivated to test for HTLV-1. Better linkage of remote clinics with HTLV-1 testing needs to occur.

Discussion

Testing of pregnant women is highly dependent on the medical practitioner, even if the woman requests a test.

Internationally and in Australia, endemic communities with HTLV-1 are missing activism, unlike HIV where they were highly mobile and visible. Guidelines can also be used as advocacy documents, but in Australia this may require translation into primary language, so people understand the care they should be receiving and can advocate for it if they are not.

There have been concerns from both Government and health professionals about balancing availability of information with alarmist messaging i.e. HTLV-1 causes cancer. Lloyd (and his project staff) hasn't seen alarm when explaining HTLV-1 in language. Has seen alarm in their doctors, but not in patients.

Shane Shincke

The patient experience

I initially presented to ASH (Alice Springs Hospital) with severe neurological symptoms and was transferred to Adelaide for further investigation. After weeks of intense testing no conclusive diagnosis was made. There was talk about MS and Neuro Muscular Disease.

Not having a diagnosis was very scary.

As a health professional, that exacerbates your anxiety.

Prior to leaving for Adelaide I was tested for HTLV-1 at ASH. The result came back positive and the results were communicated back to my treating team in Adelaide and discussed with me as a possible cause for my condition.

Nobody in my treating team could tell me anything about HTLV-1, so we had to google it.

When googling HTLV-1 – HAM/TSP, I realised that some of the symptoms described in the literature fitted my early symptoms going back two or three years (i.e. urine retention, constipation, tremors).

I had consulted with health professionals about these issues, but it wasn't linked to HAM/TSP – HTLV-1 due to lack of awareness of HTLV-1 and as a result it wasn't picked up until the disease was well advanced.

Early intervention with prednisone may have prevented spinal cord damage.

I remember how relieved I was to finally have a diagnosis, but at the same time feeling surprise that a Virus could be responsible.

Lloyd Einsiedel then led the treatment with IV steroids over three days, which made a dramatic difference, and continued with oral Prednisolone.

Currently I am on Methotrexate + low dose prednisolone dose.

There is currently no treatment available for HAM/TSP, but we are able to treat some of the symptoms related to HTLV-1 and HAM/TSP.

I returned to Alice Springs in a wheelchair.

But it isn't just about a spinal cord injury.

With HTLV-1, you always have uncertainty of what is going to happen next. There is still uncertainty how I contracted the Virus and there is uncertainty what the future may hold.

All this uncertainty makes things difficult for clinicians as well.

There certainly needs to be a better understanding and more awareness by health professionals regarding HTLV-1.

I get annoyed when doctors tell me to my face that HTLV-1 doesn't do anything.
So how did I end up in a wheelchair?

Even if you are asymptomatic, as a patient you want to know your results so you can participate in your own care, and keep your family safe.

Some diagnosis can be scary to tell patients, but we don't just send them home after telling them: "you've got cancer".

We walk with our patients and support them through the difficult times.

There is a lot we can do, with the little that we know about HTLV-1, to support and advise patients living with HTLV-1.

Living with HTLV-1 isn't glamorous. I think a lot about how I got it. What could I have done differently?

Research is important, and I'm encouraged by the Governments quick movement on this. It is so hopeful to know that all the people around this table are working on it and passionate about it.

I believe advocacy is a very important part of this, and that is what I have to offer to the work on HTLV-1.

Discussion

Haven't yet developed patient information pamphlets in language. Translation is currently done from plain English on site. 15 different languages are used in Central Australia. Joel is developing health literacy toolkits (iPad which can be used for this).

The funding is already committed, and is not dependant on Government in power. The funding is moving to be directly administered by the CMO. 2 years, $8 million.

Could HTLV-1 be elevated to priority funding through NHMRC and MRFF?

Joel: Remember that people are sitting in Central Australia right now, without information, transmitting the virus to their loved ones and children. Transmission is ongoing, right now, and is preventable.

Next steps

1. National guidelines – writing group, budget proposal from ASHM
2. Indigenous reference group – including affected communities. Must acknowledge existing structures with ACCHOS
3. Public health response? **No data** that this is a benign infection
4. Research – lots of options, need to be prioritised
5. Defining endemic area – WA?
6. National surveillance – should this be a nationally notifiable condition?